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PLATONISM OR ARISTOTELIANISM?

A CONTRIBUTION TO THE HISTORY OF MEDICINE AND SCIENCE

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It is not astonishing, regardless of the reasons given in detail, to meet with the contention that the physician *qua* physician can under no circumstances be a Platonist, or that if he is a Platonist and not an Aristotelian, he certainly is not a good doctor.[1] The claim that Platonism is destructive of a scientific attitude, whereas Aristotelianism is productive of it, is, nowadays, a familiar one in regard to all branches of learning. To be sure, the opposite stand is also taken; elaborate appreciations of Platonism and its positive influence on the development of science are given; yet Platonism is on the defensive. Generally speaking, it seems well justified to state: "Though there are honorable exceptions, it is currently taught that Platonism is the antithesis of the scientific spirit and that Plato is a reactionary in relation to the evolutionary and mechanistic philosophies of the pre-Socratics, and a dreamer, spinning the world out of his inner consciousness, as contrasted with the fact-loving Aristotle." [2]

[1] Cf. H. Silvette, Medicine in Utopia, *Bulletin of the History of Medicine*, 7, 1939, pp. 1013-18. Cf. however G. Kasten Tallmadge, Misconception of a Utopia, *ibid.*, 8, 1940, pp. 666-678.

[2] P. Shorey, Platonism and the History of Science, *Proceedings of the American Philosophical Society*, 66, 1927, p. 161. Nobody interested in the question at stake

In science and its history, then, just as in philosophy and in political theory, Aristotelianism is likely to be represented, and to be believed in, as *the* truth. The Aristotelians are winning the day, and since " every man is born an Aristotelian or a Platonist," as Coleridge holds,[3] one is inclined to conclude that nature has somehow decided the issue. Yet there is still a slight chance left for stemming this predominant trend of thought. The Aristotelians as Aristotelians and scientists are wont to cherish facts. A restatement of facts, showing that Platonism is not, and has never been, the antithesis of science, may therefore help in bringing about a change of heart in the Aristotelians. Even Coleridge, though he was " sure that no born Platonist can ever change into an Aristotelian," went only as far as not to " think it possible that anyone born an Aristotelian can become a Platonist." But what may become possible or impossible one cannot foretell, potentiality being, so to say, a function of actuality. No doubt, the facts to be recounted have been pointed out before, and many times too. Yet truth and knowledge, no matter how firmly established, are bound to perish, says Aristotle; but, so he adds, they can be recovered again and again. It is therefore with some hope at least that I dare take up the subject once more.

Plato and physic are incompatible; Plato has a lowly opinion of physicians—the one assumption is apparently based on the belief, not proved but rather presupposed, that Plato lives in a " twilight of abstractions " and is motivated by a real " hatred of a fact "; the other is elaborated on with various reasons.[4] Only the first contention, however, is, I think, important; the second, even if correct, would be quite irrelevant. Nevertheless, in order to dispose of the argument and its possible consequence, I must state that in my opinion Plato never disparages the merit of physicians and that

can afford to disregard this paper of Shorey's who, being a philologist and historian, expressly writes for scientists and carefully considers the scientific problems of today.

[3] S. T. Coleridge, The Table Talk and Omniana, July 2, 1830.

[4] Silvette, *loc. cit.*, pp. 1014 ff.; the whole argumentation as given in this paragraph refers to statements of Silvette, who, in his general thesis, shares the point of view held by N. Douglas, *Old Calabria*, ch. 38, The Sage of Croton.

therefore it is not necessary to " discount " his remarks as those of a man who does not understand anything of medicine. I have no defense to offer for the metaphysician Plato who " in the nine grades of human existence into which Platonic souls pass " places the physician in the fourth. I leave it to the political theorist Plato that in his state he wishes to have physicians who not only have suffered from diseases but are not quite healthy, because he thinks that they would make better doctors. Again, it is the responsibility of the political theorist Plato that he rejects the modern type of medical care as initiated by Herodicus and declares himself in favor of the older Asclepiadean medicine as he sees it. Whatever the merit of his decision that only those should be cured who afterwards can still do useful work, such an attitude does not imply any hostility toward medicine as such, or any depreciation of the physician's value. Moreover, many other passages in the Platonic dialogues testify to Plato's high esteem for medicine and for the medical men (cf. especially *Charmides* 156 b ff.; *Laws* 720 a ff.). Last but not least, Plato admires Hippocrates and the Hippocratic method which, as the correct procedure, he pretends to follow in his own inquiries (*Phaedrus* 270 b ff.). This fact alone should make it impossible, I think, to speak of any contempt for doctors on Plato's part, and it should suffice to show that even a man of good health until a ripe old age can sometimes think of medicine as very necessary and useful or, in other terms, that Plato is not—" Mr. Day." [5]

But, as I said before, all these considerations are of minor importance. The real issue is not Plato's personal like or dislike of physicians; it is the question of whether there is in fact a specific incompatibility of Platonic philosophy and medicine on the one hand, and a specific affinity of Aristotelian philosophy and medical thinking on the other.[6] That such a thesis should be proposed without any reservation is very strange indeed. The Galenic system, for more than a millennium and a half the dominating medical system, which to be sure served its purpose quite well, is based on the integration of Platonic philosophy into natural science; Galenic medicine is Platonic,

[5] Silvette, *loc. cit.*, p. 1018: " Indeed, while rereading my medical notes on the *Republic* I was reminded of Mr. Clarence Day's father."

[6] Silvette, *loc. cit.*, p. 1014.

at least in the eyes of Galen.[7] To Galen it is Plato, not Aristotle, who agrees with Hippocrates in the correct understanding of the bodily and psychic powers, in the correct explanation of diseases; it is Plato, not Aristotle, who shares with Hippocrates the right concepts of dynamism and of teleology. Galen, then, is a Platonist; yet he was certainly not blinded to the importance of facts. On the contrary, he prided himself upon his observations and he took even Plato and Hippocrates to task whenever they seemed not to stand the criticism of facts. Thus, for Galen and his followers, Platonic philosophy was the foundation of scientific medicine. It is true, on the other hand, that the revival of Aristotelianism in the late Middle Ages did by no means enhance a "scientific attitude," if by that concept emphasis on factual knowledge is indicated. Aristotelianism, at that time at least, brought about scholasticism and the reign of extreme dialectics, in medicine no less than in the other branches of learning. From a historical point of view, therefore, the unqualified antithesis of Platonic thinking and medicine is certainly incorrect; they are not necessarily contradictory.

But at this point an objection may be raised: even if all that I have said is true of ancient and medieval medicine, modern medicine, being a part of modern science, must be anti-Platonic since modern science itself cannot be reconciled with Platonism. Such an objection is to be taken very seriously and indicates at the same time how the question really stands. If Platonism and modern science are incompatible, then, and only then, are Platonism and modern medical science also far apart. It is therefore necessary to turn to the discussion of the problem whether Platonism and modern science are antithetic. Two statements of Plato's have proved to be the main "stumbling blocks" for the interpreter, and the correct evaluation of their bearing on the relation of Platonic philosophy to science is still much discussed: the one is Plato's insistence that reality cannot be comprehended by scientific laws, the other is his rejection of observation as a means of attaining adequate knowledge.

As regards Plato's concept that the explanation of the world of phenomena can be given only with the probability inherent in a likely

[7] This attitude of Galen's is most clearly demonstrated in his *De placitis Hippocratis and Platonis.*

story and incomparable to the certainty of logical or mathematical knowledge (*Timaeus* 29 b ff.), there is no reasonable doubt about the difference of such a belief from the attitude of the modern scientist. It may be true that Plato writes his "prose-poem" of the world-creation taking into account the scientific ideas of his time, and that in his speculations he anticipates some of the most modern scientific ideas of today [8]—the main point remains, I think, that he tells a poetical story where one expects him to give a scientific account, and that scientific explanations for the problems in question seem impossible to him. It is of no use to gloss over these difficulties. Nor have I any desire to deny that Plato, as regards facts, is most critical of their value and of that of observation. His words (*Republic* 529 a ff.) [9] seem to me an unequivocal rejection of observation as a basis of attaining astronomical knowledge in particular, and as one must conclude, of knowledge in general. Even apart from what Plato says here, it is certain that he is not interested in facts. It will not do, I think, to point to the richness of facts to be found in his dialogues,[10] though this would be enough to discard the alleged Platonic "hatred of a fact." Yet whatever the number of observations in Plato's writings, however favorably they may compare with those of Aristotle, the use which Plato makes of them is not that of scientific exploitation. Plato's attitude toward the world of phenomena is righly characterized by Kant's statement: "The light dove, cleaving the air in her free flight, and feeling its resistance, might imagine that its flight would be still easier in empty space. It

[8] Cf. Shorey, *loc. cit.*, p. 163 ff., who overemphasizes this point and hardly does justice to the fundamental difference of methods. The same is true of A. E. Taylor, *Plato, The Man and his Work*, 1936, pp. 440 ff.; 456, note 1.

[9] Cf. Plato, *The Republic*, with an English translation by P. Shorey, The Loeb Classical Library, II, 1935, pp. 179 ff., where the modern discussion of the scientific import of the passage is most conveniently summarized in the annotations. Shorey, Proceedings, *loc. cit.*, pp. 171 ff., seems somehow to differ in his evaluation of Plato's words. Is it not sufficient to say that Plato "is in some sort predicting the mathematical astronomy of today. That is of course not the whole of our modern astronomy. But it exists and is a fulfilment of Plato's prophecy" (*loc. cit.*, p. 172). Such a statement, even if true, does not do away with the Platonic rejection of facts. I do not believe either that only "a hasty modern reader" can mistake Plato's words for a repudiation of facts and observation as basis of understanding (*ibid.* and p. 173).

[10] Contrary to Shorey, *loc. cit.*, p. 163 and p. 166.

was thus that Plato left the world of the senses, as setting too narrow limits to the understanding, and ventured out beyond it on the wings of the ideas, in the empty space of the pure understanding." [11] Plato knows the world of facts, to be sure, but he leaves it behind, he even transgresses it in his thought, delving into the beyond. If this is the Platonic ethos, it is certainly not that of the modern scientist.

But there is another aspect of Platonic thinking in which Plato and the modern investigator do agree: it is Plato's recommendation of arithmetic and measurement by which alone reliable knowledge is guaranteed, his insistence on mathematical methods. He says: "If arithmetic and the sciences of measurement and weighing were taken away from all arts, what was left of any of them would be, so to speak, pretty worthless . . . All that would be left for us would be to conjecture and to drill the perceptions by practice and experience, with the additional use of the powers of guessing, which are commonly called arts and acquire their efficacy by practice and toil" (*Philebus* 55 e).[12] In other words: the mathematician Plato is "up-to-date." No doubt these and similar utterances, at least in their intention, "differ little from Lord Kelvin's statements that he understood a thing only when he could construct a working model of it, and that if you can measure a thing and express it by number, you have some knowledge of it, otherwise not; from Kant's declaration that the only part of any theory of nature that is scientific in the strict sense of the word is the quantity of mathematics which it contains; from Clerk Maxwell's statement that progress is symbolized in the clock, the balance and the foot-rule." [13] However, since the belief in the predominant value of mathematical understanding is also Platonic, it follows that the current rejection of Platonism as anti-scientific is based on an incorrect oversimplification of Platonic thinking. In reality, Platonic philosophy and modern scientific thought are not diametrically opposed but rather overlap in part.

[11] I. Kant, *Critique of Pure Reason*, Introduction, III (translated by N. K. Smith, 1929, p. 47). In his analysis of the Platonic method G. H. Lewes (*Aristotle, a Chapter from the History of Science*, 1864, p. 107) refers to this Kantian passage. Lewes' book is strangely neglected in the modern discussion.

[12] Plato, *Philebus*, with an English translation by H. N. Fowler, The Loeb Classical Library, 1925, p. 359; cf. also *Republic* 602 d, and for the historical importance of these statements for the development of modern science below, p. 764.

[13] Shorey, *loc. cit.*, p. 177.

To be sure, Platonism is not exhaustively defined by the characterizations given so far. There is Platonic love, the eternal subject of certain Platonists, or of the Neo-Platonists of the Renaissance, which has inspired philosophers and poets alike; there is mysticism which claims to be Platonic, even superstition to which the same name is given.[14] But as far as science and its history are concerned, these wrong or right conceptions of Platonism have never been important. It is not Plato's personal relation to scientists, or the supposedly scientific character of late Platonic philosophy, I think, which is responsible for the productive influence of Platonism on science. Plato, though much interested even in specific scientific problems, remains all his life a dialectic philosopher.[15] It is rather the scientists themselves who have been appreciative of the scientific trends in Platonic philosophy and have apprehended as "Platonism" that part of Platonic thinking which is a stimulus to the study of nature and to mathematical inquiry. In antiquity the *Timaeus* becomes the foundation, not of mythology, but of natural philosophy, as this term is understood at that time. Music and mathematics are essentially Platonic; in astronomy, too, many doctrines of Plato, and some of the most important ones at that, are retained. The prominent rôle played by Platonism in the natural studies of the Middle Ages has become increasingly more evident.[16] In that period it is the

[14] This side of Platonism has been well characterized by Shorey (*loc. cit.*, p. 161): "The association of Platonism with superstition is an historical fact and perhaps a natural tendency . . . The later Neo-Platonists practised levitation . . . The witty Lucian . . . represents a Platonic philosopher as swallowing all the ghost-stories which the Epicurean rejects. No wonder, says Lucian smartly; a man whose eyes are sharp enough to discern the Platonic ideas can of course see spooks. The indictment, then, is partly true of historical Platonism. But it does not fairly fit Plato." In his book (*Platonism Ancient and Modern*, Sather Classical Lectures, 14, 1938) Shorey rather neglects the scientific influence of Platonism, dealing almost exclusively with the literary influence; this is especially true of the chapter on the Renaissance (pp. 118 ff.).

[15] In this respect the stand taken by E. Howald (*Die platonische Akademie und die moderne Universitas Litterarum*, 1921) seems to me the right one. Cf. also, E. Frank, *American Journal of Philology*, 61, 1940, p. 171, concerning the essentially unchanged character of Platonic philosophy in its late form.

[16] And this is the case although the history of medieval science has not yet been studied carefully enough to warrant a substantiated judgment in all details. Cf. Ch. H. Haskins, *Studies in the History of Mediaeval Science*, 1927, p. 88; and above all Cl. Bæumker, *Der Platonismus im Mittelalter* (1916; reprinted and

natural scientists who feel attracted by Platonic ideas; it is above all the Platonists who try to understand nature, who study mathematics. Finally, that modern science has been developed in close connection, not with rediscovered Platonic books, but with rediscovered Platonic concepts, is a fact almost too well known to be mentioned.[17] Galileo quotes Plato as the authority for the value of mathematics, Kepler defends his new theory with a reference to Plato. Modern mathematical science, then in spite of its non-Platonic concept of natural laws, in spite of its non-Platonic insistence on the verifying experiment, is also in agreement with fundamental Platonic ideas. As long as modern scientific thinking remains dependent on the work done by men like Galileo and Kepler, it can never be un-Platonic. Platonism anti-scientific? Neither the Platonic dialogues nor the history of science bears out such a verdict.

The one term in the common antithesis of Plato and Aristotle being subject to material changes, should the other have to be modified also? Aristotle, the protagonist of the cause of the moderns—is such a contention convincing? To discard for the moment Aristotle's indifference toward mathematics and his very Platonic concept of natural laws as comprising either the necessary or the usual though not the accidental,[18] even the "fact-loving" Aristotle is hardly to the modern heart's desire. The old Aristotle, the master of biology and natural science, still says: "Of things constituted by nature some are ungenerated, imperishable, and eternal, while others are subject to generation and decay. The former are excellent beyond compare and divine, but less accessible to knowledge. The evidence that might throw light on them, and on the problems which we long to solve respecting them, is furnished but scantily by sensation; whereas respecting perishable plants and animals we have abundant

amplified in Cl. Bæumker, *Studien und Charakteristiken zur Geschichte der Philosophie*, Beiträge zur Geschichte der Philosophie und Theologie des Mittelalters, 25, 1928, Heft 1-2, especially pp. 153 ff.) who summarizes the work which has been done so far, but unfortunately is scattered over innumerable special investigations.

[17] The references are too many to be enumerated here. Short survey, E. Cassirer, Die Antike und die Entdeckung der exakten Wissenschaft, *Die Antike*, 8, 1933, pp. 276 ff.; more detailed the same, Individuum und Kosmos in der Philosophie der Renaissance, *Studien der Bibliothek Warburg*, 10, 1927; cf. also Shorey, *loc. cit.*, p. 180.

[18] Th. Case, *Brit. Encyclop.*, 11 ed., s. v. Aristotle, p. 517 b.

information, living as we do in their midst, and ample data may be collected concerning all their various kinds, if only we are willing to take sufficient pains. Both departments, however, have their special charm. The scanty conceptions to which we can attain of celestial things give us, from their excellence, more pleasure than all our knowledge of the world in which we live; just as a half glimpse of persons that we love is more delightful than a leisurely view of other things, whatever their number and dimensions. On the other hand, in certitude and in completeness our knowledge of terrestrial things has the advantage. Moreover, their greater nearness and affinity to us balances somewhat the loftier interest of the heavenly things that are the objects of the higher philosophy." [19] There are, then, according to Aristotle, two different realms of "facts," and though the study of every one of them is interesting and praiseworthy, the value of such studies is incomparable. Such a belief, however, is certainly not similar to that of the disinterested researcher for whom facts are valuable for fact's sake without any discrimination; it is not like the modern resignation to the world of phenomena beyond which there exists no other, at least none the existence of which can be proved scientifically. Moreover, Aristotle does not "catalogue" the facts which he collects; [20] the description of facts in his intention is only a preparatory undertaking, either "natural history, preparatory to natural philosophy, as in the *History of Animals* preparatory to the *De Partibus Animalium*, or what we call civil history, preparatory to political philosophy, as in the 158 Constitutions more or less preparatory to the *Politics*." [21] And the content of natural philosophy or political philosophy? It is the investigation of causes in which the formal cause proves to be the essential one as compared with the material conditions. In fact form, although it is recognized *a posteriori*, exists prior to matter; truly scientific research proceeds in syllogisms, in deductions, from the determining principles to the

[19] *De Partibus Animalium*, I, 5, 644b 22 ff. (The works of Aristotle translated into English [W. Ogle], V, 1912, Oxford.)

[20] Contrary to Shorey, *loc. cit.*, p. 163, who besides reduces the difference of interest in facts as shown by Aristotle and Plato to the difference between the mathematician and the biologist "who naturally collects more little facts"; but cf. above p. 761.

[21] Case, *loc. cit.*, p. 521b.

individual data. In short, although Aristotle does not venture out beyond this world on the wings of the ideas, he is not the captive of sense perception and observation either. He is the " philosopher of facts " [22] who in an imposing edifice subsumes the data under general principles which are based on the evidence of speculative reasoning. In spite of all his emphasis on facts which seems modern, he is not a modern scientific observer of phenomena.

That factual investigation is not the essential part of Aristotelian philosophy is brought out most clearly by the relation of Aristotelianism to the development of science. In antiquity those men who dedicated themselves to a direct and unbiased study of the phenomena, the scientists of the second and third generation after Aristotle are not Aristotelians. The Alexandrian schools, although originally connected with the Peripatos, sever the " link between science and philosophy," that is between science and Aristotelian philosophy. This statement is true of all sciences, last but not least of biology and medicine.[23] Even the appellation ὁ φυσικός, which was given the second successor in the Lyceum, was intended to emphasize the departure of the " naturalist " Strato from the principles of the founder Aristotle. Why so, if Aristotelianism itself is conducive to the observation of phenomena, to a scientific attitude? Or again, when Aristotelianism in its pure form had been restored during the twelfth century, logic and speculative thought became supreme. The " twilight world of abstractions," the " hatred of a fact," if one wants to indulge at all in such hyperbolic expressions, can be predicated of these most Aristotelian centuries of the Middle Ages with

[22] Case, *loc. cit.*, 517b; for the scientific method in general: Th. Case, *Scientific Method as a Mental Operation* (Lectures on the Method of Science, ed. by T. B. Strong, Oxford, 1906, pp. 1 ff.); W. D. Ross, *Aristotle*, 1924, pp. 41 ff.

[23] W. Jaeger, *Aristotle*, translated by R. Robinson, 1934, pp. 404-05: " Alexandrian science is the spiritual continuation of Aristotle's last period. There the link between science and philosophy was definitely broken; the infinitely refined technique of Ptolemaic research dispensed with the stable intellectual centre that Aristotle's detailed work had possessed in his great spiritualist view of the universe. On the other hand, the most important discoveries of ancient science are due to this separation, which was a necessary liberation of research. It was now that medicine and natural science, together with exact philology, attained their greatest flowering. They were represented by figures like Aristarchus, Aristophanes, Hipparchus, Eratosthenes, and Archimedes. From the standpoint of Aristotelian philosophy and science, of course, all this is but half of the intellectual realm; . . . "

greater adequacy than of any time before or after.[24] It is therefore against the Aristotelians, as they call themselves, that the propagators of modern science must fight; it is Aristotle's authority which has to be broken, so that not only mathematics but also observation and experiment can get the upper hand of bookish and scholastic knowledge. Aristotelianism then must be something more than "love of facts." That that is so, is a fact easily disregarded by those who are interested in Aristotle's biological works. Even in the sixteenth and seventeenth centuries when the philosopher Aristotle is almost forgotten or acclaimed only by theologians, the biologists still study his books and take delight in the material which they find therein.[25] The same is true of the eighteenth and nineteenth centuries when the aesthetic critic Aristotle and also the metaphysician Aristotle have been rediscovered: the biologist Aristotle remains in the foreground, his biological writings still are the storehouse of information. Men like Darwin or Huxley, therefore, proclaim Aristotle's authority, at the same time debasing and dethroning Plato.[26] Had the 158 constitutions survived which Aristotle collected, economists and sociologists would probably join the chorus and affirm that Aristotle was the first professor of political theory. But all such assertions overlook the truly Aristotelian point of view, that of the metaphysical ascendency over facts. Aristotle opposed to observation? I do not

[24] J. Hjort, a scientist, not a historian, says (*The Unity of Science*, 1920, pp. 14-15): "Throughout the Middle Ages, when thought was theological, men laid the chief stress upon his (sc. Aristotle's) logical system, his ideas, his works. The paucity of available facts had to be counterbalanced by a wealth of theorising. Instead of seeking evidence of the teleological principle in nature, which Aristotle after all did to a great extent, men sought it in the world of thought alone. So it came about that in course of time the teaching of Aristotle became a hindrance to the progress of science."

[25] Cf. Th. E. Lones, *Aristotle's Researches in Natural Science*, 1912, pp. 4 ff.

[26] Cf. the famous statement of Darwin (*The Life and Letters of Charles Darwin*, III, 1887, p. 252): "From quotations which I had seen, I had a high notion of Aristotle's merits, but I had not the most remote notion what a wonderful man he was. Linnaeus and Cuvier have been my two gods, though in very different ways, but they were mere schoolboys to old Aristotle." But Darwin adds, and these words are usually not quoted: "How very curious, also, his ignorance on some points, as on muscles as the means of movement. I am glad that you have explained in so probable a manner some of the grossest mistakes attributed to him." Besides contrast T. H. Huxley, *Hume* etc., 1897, pp. viii-ix with Huxley, *Science and Education*, 1897, p. 152.

say that. He is certainly a descriptive writer of the first rank but one must never forget for what purpose the description is meant. The fact that Aristotle starts from observation does not make of him a modern scientist or a scientist at all; for he begins with the phenomena only in order to ascend to metaphysical principles.

This brief and very fragmentary survey of Platonic and Aristotelian ideas, as far as they concern scientific thought, may suffice to show that the antithesis of Platonism and Aristotelianism as it is usually formulated is not tenable. "The dreamer Plato," or "Plato, the metaphysical poet," or, *horrible dictu*, "Plato, the representative of the cults,"[27] the "fact-loving Aristotle"—all such concepts are false indeed because they are unfair abstractions or wholly inadequate to the facts. Nor is it possible to oppose "the philosopher Plato" to "the scientist Aristotle";[28] both are philosophers, even if scientific research and the evaluation of facts are differently accentuated in their systems. As regards the modern scientist, who examines the Platonic and Aristotelian philosophies in order to find out what they mean to him and to his work, he will find in both ideas which are incongruous with his own conceptions, and others with which he can agree. Whether there is, in fact, an irreconcilable opposition of Plato and Aristotle in their philosophical outlook, as has been claimed in antiquity and as is claimed nowadays—from the point of view of the modern scientist such an antithesis does not exist, or it exists only in a different sense. Platonism and Aristotelianism, both can be stimulating for him, as they have been for many an earlier generation, though in various ways. Plato will be the eternal inspiration of the mathematician, Aristotle that of the descriptive scientist or humanist. To be sure, such a concept of Platonism and Aristotelianism is also an abstraction which oversimplifies and emphasizes certain features to the exclusion of others of equal or even greater importance. Yet it at

[27] R. Spillmann, quoted by Silvette, *loc. cit.*, p. 1014, note 2.

[28] That is what is really meant by Coleridge's distinction between born Aristotelians and Platonists (cf. above, p. 758), as is clear from the following words: "Yet what a mind was Aristotle's . . . the parent of science, properly so called . . . but he confounded science with philosophy, which is an error."

least symbolizes trends which are real characteristics of Platonic and Aristotelian thinking and as such have been associated throughout the centuries with the history of Platonism and Aristotelianism.

I do not think that it could do much harm if the terms "Platonism" and "Aristotelianism" continued to be used in a way which is not at all justified by the historical data. Yet it may be appropriate to recall Lange's statement:[29] "Hand in hand with philosophical goes historical culture. Next to the contempt of philosophy, a Materialistic trait appears in the lack of historical genius, which is so often combined with our scientific inquiry. Nowadays a historical view is often supposed to mean a conservative one. This results partly from the fact that learning has often allowed itself, for gold and honour, to be misapplied in supporting obsolete powers, and in serving predatory interests, by pointing to departed splendours and the historical acquisition of rights hurtful to the common weal. Natural science cannot easily be misused for such purposes. Perhaps, too, the continual call for renunciation imposed by science has a bracing effect on character. In this aspect the unhistorical sense of men of science could only redound to their glory. The other aspect of the matter is, that the lack of historical apprehension interrupts the thread of progress as a whole; that trifling points of view control the course of investigations; that the depreciation of the past is accompanied by a Philistine over-estimate of the present condition of science, in which the current hypotheses are regarded as axioms, and blind traditions as the results of investigation."

[29] F. A. Lange, *History of Materialism*, translated by E. Ch. Thomas, II, 1880, p. 333.

SAINT HILDEGARD, TWELFTH CENTURY PHYSICIAN*

GERTRUDE M. ENGBRING, M. D.

It is obvious that in general the medical profession has been a masculine profession. Men have been the leaders in developing, conserving, and handing on our knowledge of medicine and surgery. An occasional Madame Curie comes into the forefront from the laboratory side; or now and then some exceptional woman makes her mark as a practicing or teaching physician. But the long history of medicine, from Hippocrates onward, is so much a roll of masculine names that it may almost be shocking to claim for a woman the title of the most renowned medical writer of her century. To many persons, the claim is all the more startling when the century is the twelfth century, back in what ill-informed people, in spite of all the fine work of Maitland, Gasquet, Rand, Haskins, Taylor, and Thorndike, to mention only writers in English, still call the Dark Ages, in which women were shut off completely from intellectual activity.

Yet the claim has been well established for Hildegard, the Benedictine Abbess of Rupertsberg, near Bingen. Both the volume of her published work and the interest of students in it are considerable, may even be thought of as astonishingly large, when one recalls how long ago she wrote, and how greatly medical studies tend to look forward rather than to weigh the past. Some of her works were printed as early as 1513, and have gone through many editions. One of her medical writings was printed in 1533, and a critical edition of it included in Migne's collection of *Patres Latini*.[1] Scholars have continued to discuss her writings critically even up to our own times. The bibliographer Chevalier lists sixty-six studies about her, although he does not include the abundant discussions published during the twentieth century.[2] One of her editors, Paul Kaiser, thought that "her medical skill contributed more to her popular reputation

* Read at the Medical History Club of Loyola University Medical School at its February, 1940, meeting.

[1] Cols. 1117-1352 of volume 197, Paris, 1855.

[2] Ulysse Chevalier, *Repertoire des Sources Historiques du Moyen Âge*, 2d ed., 4 vols., Paris, 1903-1907; *Bio-Bibliographie*, I, 2153-2154.

for saintliness than all her writings." [3] For although she was never canonized, Hildegard is set down as a saint in the Roman Martyrology, and is dealt with at great length by the Bollandists.[4]

The outlines of Hildegard's life are clear enough, both from her own writings, and from the investigations of scholars. She was born at Böckelheim, a village in the county of Sponheim, a district between the rivers Moselle and Nahe, in the year 1098. Her father, Hildebert, was a soldier; her mother was named Mechtild; both were probably of the petty nobility. When she was eight years old, Hildegard was placed in the Benedictine convent of Disibodenberg, on the Nahe, as an oblate, to become a nun when of the canonical age. There she got her education, the exact extent of which we do not know. For instance, she learned enough Latin to read the Church Office; but she never did become proficient in Latin, and even late in life had to have a monk polish up her Latin dictation. She implies, in a statement made to the monk Guibert when she was more than seventy years old, that she knew how to write " rude Latin." [5]

About 1136, she was made Prioress of the little convent, and some time later its Abbess. In 1147, she took eighteen nuns of the convent, now crowded for room, and founded a new convent at Rupertsberg, at the mouth of the Nahe, opposite Bingen; and hence it is as St. Hildegard of Bingen that she is usually known. She was Abbess at the Rupertsberg for more than thirty-one years, dying on the 17th September, 1179, at the age of eighty-one. The latter half of her life brought her into contact with popes and princes and notables, resulting in an immense correspondence.[6] She was consulted almost as an oracle. She traveled extensively. She built a branch convent at Eibingen. Although in constant ill health all through her long life, she cured multitudes of the sick. She was revered as a saint and seer for many years before she died. She was the inspira-

[3] See Lynn Thorndike, *A History of Magic and Experimental Science*, 4 vols., New York, 1923; II, 126.

[4] *Acta Sanctorum*, September, vol. V (Venice, 1770); pp. 629-701. Although steps toward her canonization were begun in 1233, her cultus and insertion in the martyrologies date only from the fourteenth or fifteenth century. *Ibid.*, 679 C.

[5] See the English translation of the passage from Pitra's *Analecta*, VIII, 332, in Henry Osborn Taylor, *The Mediaeval Mind*, London, 1927; I, 465-466.

[6] Her letters are in Migne, *P. L.*, 197: 145-382.

tion and exemplar, perhaps not always with the best results, of St. Elizabeth of Schönau.[7]

Hildegard was a mystic, favored even from her childhood with strange supernatural states of prayer, difficult to describe or evaluate. A number of her writings purport to contain the visions that came in her mystic prayer, and that she afterward dictated in a mixture of Latin and German. Even if there be no question that her visions were genuine, there is evidently a chance for fine confusion here. How much of these writings is really the product of mystical revelations? How much is a mingling of visioned truths and her own knowledge or opinion? How much is the pious embroidery of the monk who acted as secretary?[8] Hildegard is repeatedly explicit in her statement that she saw in vision all that she dictated; but she makes this statement only for three of her five major works, not for the two distinctly medical works. It is with these two medical works that we are here concerned.

Yet it must be said in passing that the three works which record her visions contain a good deal of medical and other science, and that some of the ideas there expressed about anatomy, physiology, and pathology reappear in her medical writings. Since not a few of those ideas are demonstrably false, it is quite evident that they were not revealed by God to Hildegard. The simplest explanation might

[7] Elizabeth was born of a humble family in 1129, near Treves. In 1141 she became an oblate in the Benedictine (not Cistercian) double monastery at Schönau, where she made her profession in 1147, and became Abbess in 1157. She died there, 18 June, 1164. Like Hildegard, she was never canonized, but is in the Roman Martyrology. She had ill health, like Hildegarth; she claimed to have visions, like Hildegard; she dictated her visions, like Hildegard; she even borrowed a title for one of her books, *Liber Viarum Dei*, from the *Scivias* of Hildegard. Her secretary was her brother Egbert, at first a diocesan priest, later a Benedictine at Schönau, and Abbot of the double monastery, for monks and nuns. He wrote, as for his sister, three works, which have been completely edited only in 1884, by F. W. E. Roth, although parts of them were published together with some of Hildegard's works in the Schott edition, Strassburg, 1513. Elizabeth, or her secretary-brother, did much to establish the fraudulent legend of St. Ursula and the eleven thousand virgins of Cologne. Her visions are printed by the Bollandists, *Acta SS.*, October, vol. VIII, pp. 165-173. See also *ibid.*, June, IV, 499 sqq., and October, IX, 81 sqq., for accounts of her life and works.

[8] Read the careful, measured, and modest account of her visions in Henry Osborn Taylor, *The Mediaeval Mind*, 2 vols., 4th edition, London, 1927; I, 464-475.

seem to be this: granting the genuineness of Hildegard's visions, they represented moral and religious truths to her in a super-sensory way; in order to translate those truths into a humanly intelligible form, Hildegard made use of illustrations and analogies drawn from her own scientific knowledge got by study and observation; hence the authenticity of her visions affects at most only their moral and religious truths, not their anatomical and physiological illustrations. These three works are: *Scivias* (a portmanteau word for "Sci vias Dei—Know thou the ways of God"), which was written between 1141 and 1151; *Liber Vitae Meritorum*, written between 1158 and 1163; and the *Liber Divinorum Operum Simplicis Hominis*, written between 1163 and 1170, that is between the sixty-fifth and seventy-second years of her age.[9] We have no further concern with them in this paper.

According to the Benedictine Abbot Trithemius,[10] the first of Hildegard's medical writings was done during the eight years, 1151

[9] The first and third of these books of visions have been reprinted in Migne, *Patres Latini*, vol. 197; the *Scivias*, from the edition of Faber Stapulensis, printed by Etienne, Paris, 1513; the *Liber Divinorum Operum* from Gian Domenico Mansi's edition of Etienne Baluze's *Miscellanea*, Lucca, 1762, II, 337 sqq. The *Liber Vitae Meritorum* seems never to have been printed until 1882, when Cardinal Pitra, the librarian of the Vatican, included it in volume VIII of his *Analecta Sacra*.

[10] Johann Heidenberg, called Trithemius from his birth-place, Trittenheim, was born in 1462, became a Benedictine at Sponheim in 1482, and rather astonishingly was made Abbot of Sponheim the year following. During his twenty-three years of rule at Sponheim he amassed a famous library, which had, as he claims, original manuscripts of St. Hildegard. But his monks loved him not, and he changed his abbotship to the Scottish monastery of St. James at Würzburg in 1506. There, in the next ten years, he did most of his writing, some of it spiritual works, some historical, and there he died in 1516. The Jesuit, Johann Buys, edited his spiritual writings at Mainz, in 1605. Another Jesuit, Henri de Sommal, edited his commentary of the Benedictine Rules, in 1608. Some of his historical works were published at Frankfort in 1601. But his *Annales Hirsaugienses* (Chronicle of Hirschau) was published, 2 vols., folio, in 1690. It is in the *Annales* that he gives the data about St. Hildegard. His value as an authority is debated. The Jesuit Adam Tanner (1571-1632) defended him, in *Apologeticae Orationes pro Joanne Trithemio Abbate Spanheimense*, Ingolstadt, 1630. For a list of the discussions about him, see Ulysse Chevalier, *Repertoire des Sources Historiques du Moyen Âge*, II, 4559. The Bollandists cite the *Annales* (they call it *Chronicon Hirsaugiense*) about Hildegard's writings, *Acta SS.*, September, V, 672-676 (reprinted in Migne, *P. L.*, 197: 73-84).

to 1159, from her fifty-third to her sixty-first years of age. He calls this work *Liber Simplicis Medicinae*.[11] The Bollandists think that the *Liber Compositae Medicinae* also dates from this period. The matter of fixing the exact date of composition is of secondary importance; but it evidences the uncertainty that surrounds these two medical writings. Part of that uncertainty comes from confusion about the titles of the two works; and that confusion comes from the fact that early manuscripts did not always have such distinct titles as our modern books, and from the further fact that copyists not merely tried to improve on the old titles, but sometimes juggled parts of various books together to make a new book.

As a result of that confusion about the titles of Hildegard's medical writings, Dr. F. A. Reuss, who edited one of them for the volume of Migne's *Patres Latini*, and who was careful to give the work two of the titles by which it was known, namely, *Physica*, and *Subtilitates Diversarum Naturarum Creaturarum*, did not know that this same work had still a third title, and that it was really the *Liber Simplicis Medicinae* which he set down in the list of her unpublished works.[12] In the same way, the work anciently known as the *Liber Compositae Medicinae*, and so entitled in Cardinal Pitra's edition of 1882, has now become better known under the title used in Kaiser's edition of 1903, *Causae et Curae*.[13]

[11] Trithemius also attributes three other works to this period: a Book of Exposition of the Gospels, a Song of Celestial Harmony, and *Lingua Ignota*, a sort of Esperanto.

[12] See his list of the unpublished works of Hildegard, Migne, *P. L.*, 197: 144. See also Lynn Thorndike, *op. cit.*, II, 128, and the bibliographic note on p. 125.

[13] Pitra's edition of 1882 is not satisfactory, because it is incomplete; but it was made from a good MS, which had once belonged to the Monastery of St. Maximinus, and had come through various hands to the Royal Library of Copenhagen. Other MSS were known to be preserved at Wiesbaden. When Reuss edited Hildegard's first medical work for Migne's volume published in 1855, he was aware of the existence of her second work, since he added this note: "The Reverend Ludwig Schneider, pastor of Eibingen (a place where St. Hildegard had founded a branch convent) . . . has promised that he would edit some unpublished works of the Saint, from very old manuscripts preserved at Wiesbaden." (Migne, 197: 144.) But it was left to Jessen and Kaiser to make a thorough study of her second medical writing. Paul Kaiser edited, from the Copenhagen MS, *Hildegardis Causae et Curae*, Leipzig, 1903. The full title of Pitra's edition of 1882 is *Liber Compositae Medicinae de Aegritudinum Causis, Signis, atque Curis*. Reuss had

It is possible that this variety of titles has also stimulated the modern critical spirit to question the authenticity of the medical writings long attributed to St. Hildegard. That is a most proper question, one that must stand at the head of any discussion of these writings. The Bollandist [14] who wrote the account of her works in the *Acta Sanctorum*, prudently refused to make any definite statement about the genuineness of her medical writings, on the reasonable ground that he had not studied and compared the manuscripts. But others have not been so reserved in their judgments. Singer flatly rejects both of these books.[15] On the other hand, Daremberg, a bibliographer as well as a physician, Reuss, Karl Jessen,[16] Cardinal Pitra,[17] the librarian of the Vatican, and Paul Kaiser,[18] accept both books as genuine, and give grounds satisfactory enough to convince Thorndike.[19] Space allows us only to summarize briefly the arguments for and against recognizing these books as the work of St. Hildegard.

The first difficulty arises from the absence of original manu-

no definite knowledge of this work when he published his dissertation, *De Libris Physicis S. Hildegardis Commentatio Historico-medica*, at Würzburg in 1835, or his *Der Heiligen Hildegard Subtilitatum Diversarum*, etc., *die werthvolleste Urkunde deutscher Natur- und Heilkunde aus dem Mittelalter*, in the *Annalen des Vereins für Nassau, Alterthumskunde und Geschichtsforschung*, Bd. VI, Heft 1, Wiesbaden, 1859.

[14] Jean Stiltinck, S. J. (1703-1762), *Acta SS.*, September, V, 672 D. (Venice, 1770.)

[15] Charles Singer, "The Scientific Views and Visions of Saint Hildegard," in *Studies in the History and Method of Science*, Oxford, 1917, p. 12.

[16] In *Sitzberichte Wien. Math. naturw. Klasse* (1862), XLV, i, 97-116; and *Anzeiger für Kunde der deutschen Vorzeit*, 1875, p. 175 sqq.

[17] Jean-Baptiste Pitra (1812-1889), first a diocesan priest, then a Benedictine, was made Cardinal in 1863, and librarian of the Vatican in 1869. A very erudite man, he published, 1852-1858, a four-volume collection of Patristic MSS, *Spicilegium Solesmense*. Later he planned eight volumes of *Analecta* to this collection, of which the first was published in 1876. Volume VIII contains the passages from the writings of St. Hildegard, under the title *Liber Compositae Medicinae*. The Bollandists discussed Pitra's edition, and suggested a few emendations from a Brussels MS, in *Analecta Bollandiana* (Brussels, 1882), I, 597-608.

[18] Paul Kaiser, *Die naturwissenschaftlichen Schriften der Hildegard von Bingen*, Gaertner, Berlin, 1901; and in *Therapeutische Monatshefte*, Berlin, 1902, 6, 8, 9, 11, 12.

[19] See Lynn Thorndike, *op. cit.*, pp. 128-129, for a resume of the arguments in favor of the authenticity of the two medical works.

scripts and the scarcity of very early manuscripts, a common difficulty with early writings. Singer makes much of the fact that the manuscript in the Bibliothèque Nationale, which Daremberg and Reuss edited, was written as much as two hundred years after the death of Hildegard. But, as Thorndike points out, Singer apparently did not know of the Copenhagen manuscript, which Jessen, Pitra, Kaiser, and others studied, and which, although not an original manuscript, dates from the time of St. Hildegard.

Even more important is Singer's objection that these two medical books differ so much in tone and spirit from the "ecstatic but well ordered and systematic work of the prophetess of Bingen," and that they abound in Germanisms "which never interrupt the eloquence of her authentic work." [20] An obvious answer to this objection is that the two kinds of writing, her "visions" and her homely, practical compilations of medical lore, would inevitably differ in tone and spirit as they differed in their occasion and origin; and that the Germanisms might well be a mark of authenticity in a German Abbess who was weak in Latin, and did not here have to fall back upon dictation to a Latin-writing amanuensis. The nun-physician would not have to write quite exactly as the nun-prophetess. Kaiser, who studied the Copenhagen manuscript carefully, was struck by the many points of resemblance it offered with the acknowledged writings of Hildegard.

But, although the weight of evidence and opinion is now in favor of accepting St. Hildegard as the author of the two medical works attributed to her, there can scarcely be any doubt but that her writings have suffered much from interpolations and additions in the manuscripts which we now possess. The same must be said, of course, about most other early manuscripts. But both the character of St. Hildegard's medical writings and the way in which they were written lend themselves readily to the mutations and additions of copyists, and even to combinations of parts of diverse books into one. To make this clearer, it will be well to consider briefly, first the sources of Hildegard's medical knowledge, then the character of the two books, *Liber Simplicis Medicinae*, and *Liber Compositae Medicinae*.

[20] C. Singer, *op. cit.*, pp. 12, 15.

To begin with, we must remember that mediaeval monasteries were for a long time centers of medical study and practice. In his introduction to Migne's edition of St. Hildegard's first medical work, Dr. Reuss points out how many medicinal herbs are associated with the names of Our Lord, or His Mother, or the Saints, as one indication that they derive their origin or their nomenclature from the monastic interest in the medical properties of plants.[21] His brief references trace these connections back to Carolingian times, in the *Hortulus* of Walafrid Strabo,[22] who died at Reichenau in 849, and the writings of the Benedictine Constantinus Africanus, who died eleven years before Hildegard was born.[23] He notes the few hints in her writings that Hildegard had read some of these older monastic works.[24] But it is not likely that such reading was the chief source of her knowledge of medicine as revealed in her writings.

A much more important source of her medical knowledge was

[21] *Patres Latini*, 197: 1119. This edition of St. Hildegard's *Physica*, or *Subtilitates*, or *Simplex Medicina*, was transcribed by Dr. Charles Daremberg, the librarian of the Mazarin Library, from MS No. 6952 in the Bibliothèque Nationale, and compared with the printed editions of 1533 and 1544.

[22] Walafrid Strabo ("the squinter"), a Swabian, became Abbot of Reichenau in 838. His *Hortulus* is an account in Latin verse of his cloister-garden. Migne edited his works in *Patres Latini*, vols. 113 and 114. His poems have also been edited by Dümmler in *Poetae Latini Aevi Carolini* (*Monumenta Germaniae Historica*), Berlin, 1884, II, 259-473.

[23] Constantinus was born at Carthage (hence "Africanus") about 1015, studied medicine in the East, notably at Babylon, returned to become a Benedictine at Monte Cassino. He was one of the earliest translators from the Arabic physicians. His works were printed at Basle, 1536-1539. Oudin's account of him is reprinted in Migne, *P. L.*, 150: 1559-1566.

[24] In *Physica*, Book I, ch. 51, on *Wulffesmilch* (carduus niger), Hildegard mentions "medicinarum philosophi." (Migne, *P. L.*, 197: 1149.) In Book III, ch. 58, she writes of the unguent of Hilarius (or Hilarion) the Egyptian, which cures pain in the side. (Migne, 197: 1246.) In Book VII, ch. 5, she gives "quidam philosophus" as her authority for the method of catching a unicorn by means of young maidens. (Migne, 197: 1317-18.) These are very meagre references, and do not show any wide reading. Singer remarks that she never uses an Arabic term and concludes that she had not studied such writers as Constantinus Africanus, who abounds in Arabic phrases. But he admits evidence in her writings of the influence of the School of Salerno. (*Op. cit.*, p. 18.) See also, in this connection, Donald Campbell, *Arabian Medicine and its Influence on the Middle Ages*, 2 vols., London, 1926; I, cc. vi and vii, especially pp. 105, 107, 111-112, 114, 120-122, 124, 128.

the tradition of her monastery, the knowledge of herbs and treatments of various ailments handed down, either by word of mouth, or in jottings and recipes. That tradition was already well established in the time of Hildegard, and was to begin its decay only when the development of the universities gradually made the teaching and practice of medicine a more rigorously academic affair, regulated by formal schools. It linked with the peasant woman's concern about the minor ailments of her family, and the noble lady's interest in the health of her servants and serfs. It was influenced by the position of women teachers of medicine in the School of Salerno, where the famous Trotula, more than a century before the time of Hildegard, was head of the department of women's diseases.[25] Women midwives were still predominantly charged with the responsibilities of child-birth and post-natal care.

There is no evidence that St. Hildegard ever attended a medical school. In fact, there were already ecclesiastical restrictions against even priests and monks attending lectures on either law or medicine, as tending to withdraw them from their spiritual duties as pastors of souls; and the Fourth Lateran Council was soon, in 1215, to restrict clerics in the practice of medicine when it involved "cutting or burning," as inconsistent with the gentleness of their calling.[26] It is not without significance that her medical writings ignore surgery completely, and are vague in their reference to anatomy. Surgery was not likely to have been practised by monastic infirmarians; and anatomy was still the handmaid of surgery rather than of medicine.

[25] For a brief introduction to the place of mediaeval women in medicine, see James J. Walsh, *Old-Time Makers of Medicine*, New York, 1911, Chapter VIII. At Salerno, besides Trotula, who wrote a treatise on gynecology, two other women, Abella, and Rebecca, made contributions in embryology, and Mercuriade won fame as a surgeon. There is much information about these women in the great work of Salvatore de Renzi, G. E. T. Henschel, and C. Daremberg, *Collectio Salernitana, ossia Documenti Inediti e Trattati di Medicina Appartenente alla Scuola Medica Salernitana*, 5 vols., Napoli, 1852-1859. See also D. Campbell, *op. et loc. cit.*

[26] These prohibitions were expressed in the Codex Juris Canonici, and were repeated in the Council of Tours, in 1163. In the present Code, Canon 139, # 2, forbids clerics to practice medicine or surgery without an apostolic indult. See the article, "Medicine and Canon Law," by William H. W. Fanning, S. J., in *Catholic Encyclopedia*, X, 142-143.

Moreover, we know that Hildegard, when she was thirty-eight years old, was made Prioress at Disibodenberg. Now the Prioress, who ranked under the Abbess, was usually charged with the care of the servants and workmen who, with their families, lived on the estate of the monastery. Hildegard's duties toward these dependents of her convent included care of their health, and gave her opportunity to put into practice some of the medical knowledge which was the possession of her community of nuns. From what we know of the intellectual energy of Hildegard, it is certain that she could not have taken her work as infirmarian in any slack or half-hearted way; she could not rest with anything less than mastery of whatever means of medical instruction were at her command.

Hence there does not seem to be any need to have recourse to her mystical visions to explain Hildegard's knowledge of the causes and remedies of diseases. Such an explanation is always shaky, from the very nature of mystical experiences, which are most often received in a non-sensory way, and would be doubly shaky in the case of medical pronouncements that are by no means always objectively correct.

Her medical writings were, therefore, compilations of traditional monastic observations and formulas, enlarged by her own studies and practice. They were the sort of writings which, in less skillful presentations, were common enough amongst nuns. When they were copied for use in another convent or monastery, it was most natural for the scribe to insert additions or emendations from the storehouse of traditions in his or her monastery, with the feeling that it was all part of a common fund of medical knowledge, partly drawn from books, partly a sort of monastic folk-lore.

This view is confirmed by a study of Hildegard's writings themselves. In the *Liber Simplicis Medicinae*, we can note how the old doctrines of the " humors " of the body, of its deadly " miasma," of the four temperaments, reminiscent of Galen and Aristotle, of the delicate balance, for good or ill health, between the hot and the cold, the dry and the moist, of the influences of the moon's phases, flow in and out of Hildegard's naive accounts of the medicinal value of grains and herbs and trees and flesh of animals and fishes and all the oddments used in mediaeval medicine; and in so far her work

has the flavor of the monastic library. But the homely common-sense of many of her observations, the feeling of direct experience, the constant admixture of old German words for her plants and animals, her frank simplicity, her pious interpretations, her guileless credulity, are all fragrant of the monastic garden and the monastic herb-room and the talk of nuns skilled in "simples" and recipes that are half folk-lore and half medical superstitions.

There are no marvellous discoveries here, no pride of blazing new paths for the advance of science. It is well called "The Book of *Simple* Medicine." It deals with the simple, direct, natural sources of medical treatment, primarily with food values, then with the health effects of every-day herbs and plants, and with the almost legendary uses of animals and stones and metals. It discusses wheat and barley and beans, ginger and pepper, roses and radishes, *Huswurtz* and *Wuntwurtz* and *Brachwurtz*[27] and many kinds of *Myntza*, or mint, and mushrooms and aloes. And if it puts milk and salt and honey alongside of myrrh and incense,[28] and lists eggs amongst the 213 varieties of plants that it studies, what men or women of the twelfth century were yet ready to bother their heads about such a detail of classification?

This first of the nine books that make up the work of Migne's edition[29] deals with plants, and is the longest of the nine, filling eighty-five folio columns. In the succeeding books, and in the same simple and genial way, Hildegard discusses the medicinal uses of three of the four elements, air, water,[30] and earth, and of fifty-five kinds of trees, for most of which she knows only the German names,

[27] See Book I, Chapters 42, 44, 54. The editor gives the botanical names: *sempervivum tectorum*, *frasica*, and *esula*.

[28] See Book I, Chapters 175-182, in Migne's edition. It is to be noted, as another mark of the modifications made by copyists, that the division of books and chapters varies in different manuscripts and reprinted editions.

[29] In the edition of 1533, with which Daremberg's transcription of a fifteenth century MS is collated, Book IV, on Stones, is wanting. It takes up columns 1248 to 1266 in Migne.

[30] Hildegard's notions about the element Water are very curious. The sea, she says (Bk. II, ch. 3), sends forth the rivers that water the earth, as the blood in his veins waters the body of man. Then she considers the rivers she knows, the Rhine, the Donau, the Moselle, the Nahe, and evaluates them by their origins and connections with the sea as their source.

and twenty-six precious stones, such as the beryl and sapphire and topaz and chrysolite and pearl, of which marvellous medicines were made in those days, and thirty-seven sorts of fishes, beginning with the whale, which she recognizes as a mammal, and sixty-eight kinds of birds, from the griffon to the wasp, and forty-three animals, of which the first is the elephant and the last is the ant, and eighteen reptiles, including dragons, basilisks, spiders, and turtles, and the eight metals, gold, silver, lead, tin, copper, brass (*Messing*), iron, and steel, of which she sensibly recognizes lead and brass as poisonous, and warns against eating powdered silver, but knows the tonic value of copper and iron.

Hildegard's second medical work, variously entitled *Liber Compositae Medicinae*, and *Causae et Curae*, may be called " the Etiology and Therapy " of diseases. This work does not concern itself with any attempt at classifying diseases, but rambles along rather as a series of notes and jottings accumulated over a period of years. Yet when one reads it carefully, there is evident some plan of presentation, although the plan appears to be broken and incomplete.

In Kaiser's edition,[21] the better of the two we have, the text is divided into five books, one of which, Book II, is disproportionately long, taking up three-fourths of the entire work. The first Book follows a vague plan, beginning with brief paragraphs on the creation of the world, the angels, and the human soul, the " prime matter " of Aristotle, and the fall of Lucifer, but devotes thirty-one of its thirty-three pages to a consideration of the medicinal powers of the four elements, the influence of the winds and sun and stars and planets, a sort of cosmological medicine, which she may well have got, as Singer suggests, from Isidore of Seville.

The very long Book II, 132 pages, defies summarizing or condensation. It deals with all sorts of diseases, from insanity to halitosis and the common cold; it has a good deal of Hildegard's own theory of etiology and therapy, which Singer says she elaborated from " the Hippocratic doctrine of miasma and the humors "; [22] it dwells at considerable length, through as much as twenty scattered

[21] *Hildegardis Causae et Curae*, Teubner, Leipzig, 1903. It is a duodecimo in which the text fills 243 pages.

[22] Singer, *op. cit.*, p. 15.

pages, upon procreation and birth; it discusses blood-letting and fevers and dysuria and asthma and problems of menstruation and tooth-ache and nightmare, in a rather pell-mell fashion. But through the whole book there runs one thread, often reappearing: the Fall of Adam and Eve, as the fount and source of our bodily ills. In no mean way, that thread ties the loose contents of the Book together.

Book III, a short book of only twenty pages, shows a much more definite plan. Its discussions begin with man's head (the first paragraph is on why he loses his hair) and include melancholic headache, amentia, migraine, and various other types of headache (with an odd interruption of recipes for ailments of the lungs); then take up the eye, ear, nose, and throat field; then move down to the heart, liver, and kidneys, with a medical treatment for rupture on the way; then to iliac pain, bone tumors, sterility in men and women, fistula, and ulcers; and end up with the gout. That is clearly a topical plan, going from head to foot.

Book IV, of thirty-four pages, starts out with amenorrhea and menorrhagia, but wanders as badly as Book II, goes back to colds, and difficult births, and rambles on to louse infestation and dropsy and epilepsy and the stone and leprosy and fevers, acute, quotidian, tertian, and quartan, and even throws in a little veterinary medicine, for sheep, horses, asses, pigs, and goats.

The last Book, taking up twenty-four pages, indicates some return to plan. Its opening paragraphs deal with the signs of life and of death. But it promptly becomes discursive, rambles back to the various fevers already discussed, to urinalysis, to a most shrewd study of drinking water and water for bathing (but she believes that hot springs are heated by the fires of Purgatory), and finally to a long dissertation, eight pages, on the prospects for a child conceived on each of the lunar thirty days.

At first sight, the broken plan and disturbed order of *Causae et Curae* might seem to lend force to Singer's argument against acknowledging the work as St. Hildegard's. But even apart from the likelihood of some interpolation by copyists, the imperfections of plan can be readily explained by the great probability that the work was written when St. Hildegard was an elderly woman, intensely occupied with other affairs, and able to give to her writing only

scattered moments snatched at long intervals from more pressing business. It is not easy to keep to a planned work under such circumstances.

As an illustration of how the apparent wanderings of *Causae et Curae* may not be quite without rhyme or reason, we may compare its three widely separated paragraphs on *Coryza*. The first occurs in Book II,[83] and may be translated thus:

> Sometimes disturbances of the air and other elements mount to the brain and cause an interchange of its humors and create a milky frothing through the nose and throat so that an inflammation is set up like the froth of milky water.

And she suggests only a general treatment, to prevent congestion and establish free drainage; which is not much more than the modern formula of "a couple of dozen soft handkerchiefs."

In Book IV, *De Coriza*,[84] Hildegard gets down to a more definite treatment:

> If the distress of a great discharge from the nose becomes too annoying to a man, let him take four parts of anise to one part of fennel and put them on a heated tile or thin brick and stir them together whilst they vaporize and inhale the vapor, and eat some fennel and anise with bread. Do this for three or four or five days until the discharge from the head and nose be eased. For the heat and moisture of the fennel gathers the ill-adjusted humors and the dry coldness of the anise dries them up, when these two are tempered together on a heated brick, as has been said.

The last six paragraphs of Book V, at the end of the whole work, Kaiser indicates as spurious, without, however, explaining the grounds of his opinion. Next to the very last of these is a formula *Contra Coryzam*,[85] which reads:

> If there is excessive discharge from the nose, inhale smoke from burning fir wood and the discharge will be eased and stopped. Or take charred fir wood and make a lotion of it and bathe the man's head with this and it will free the humors of his head and clear his eyes.

This may well be some favorite recipe of a copyist added on to Hildegard's work. If we reject it, the other two passages hang

[83] In Kaiser's text, pp. 134-135.
[84] In Kaiser's text, p. 190.
[85] *Ibid.*, p. 243.

together as distinct statements of etiology and therapy, leaving only the question of why they should have been so widely separated: a question answerable only by pure conjecture.

But illustrations, even if multiplied far beyond the limits of this brief paper, cannot give an adequate idea of the considerable store of mediaeval medicine contained in these two works of St. Hildegard. Her writings must be read fully to be properly appreciated. Their content is so large and so varied that there is great danger of distorting the work by selecting snippets as samples. Thus, for instance, Thorndike, who has a high opinion of St. Hildegard, and who makes a brilliant attempt to analyze her work, admits that *Causae et Curae* is a work " which it would be very difficult to summarize or excerpt." [88] More than that, he proves his statement in fact by the lop-sided result he achieves in his own summarizing and excerpting. Because of his own immediate interest in mediaeval magic, he culls the " white magic " formulas of Hildegard, which are only a tiny fraction of her writings, and enlarges their importance out of all proportion. One might gather from Thorndike that Hildegard was a sort of witch-doctor, an accusation which Thorndike himself would reject with vigor, instead of being what she really was, a sound and sensible chronicler of what the men and women of her time soberly accepted as medical science.

This brief paper pretends to be no more than an introduction to St. Hildegard's medical writings. As such, it can be summed up in these three statements: that the two medical writings, *Liber Simplicis Medicinae* and *Liber Compositae Medicinae*, under their various titles, are substantially the work of St. Hildegard; that they have no claim to a supernatural origin for the medical views they contain; and that they are of real value as evidences of how medical knowledge was preserved and spread and made available for practical use, through the labors of monks and nuns, during that long period when Europe was creeping out of barbarism and about ready to begin the great cultural revival of the Middle Ages.

[88] Lynn Thorndike, *op. cit.*, p. 129.

A HISTORY OF THE CLASSIFICATION OF HUMAN BLOOD CORPUSCLES *

(PART II)

JEAN CAPTAIN SABINE

The Two Great Schools of Hematology: the Primitive Stem Cell and its Interpretation

Two major concepts in the broadening field of hematology have affected the classification of blood cells. One is the derivation of the cell types from a primitive cell or cells in the marrow and elsewhere in the body; the other is the relationship between the blood cells and the other systems of the body, particularly the adult connective tissue. Differences in interpretation of observed phenomena have been largely responsible for the growing up of two opposed schools on the subject of the histogenesis of the blood cells. Although the two phases overlap chronologically and are not truly separable, it will be necessary, to avoid utter confusion, to discuss the interpretations regarding the primitive hematopoietic cell or cells, separately from the experimental and embryological work, and separately from the work on the relationship of the mature blood cells and the other tissues of the body.

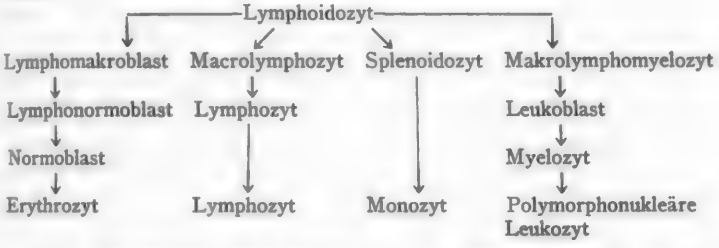
The connection between the bone marrow and the blood has been recognized for centuries. As soon as the staining techniques came into use, many observers, including Ehrlich, stained the bone marrow, and from this time primitive precursors of the blood cells were recognized in the marrow. Ehrlich described a primitive, mononuclear, large basophilic cell with a vesicular nucleus and with few or no granules. This he called a " Myelozyt," and considered it to be the specific precursor of the granulocytes. As we have noted, Ehrlich believed that some of the granulocytes were derived from " Übergangsformen " which arose either in the spleen or bone marrow. The lymphocytes he held to be an entirely independent strain, derived from the lymphoid tissue. This was the founding of the polyphyletic school, later to be led by Naegeli, Schridde, Ziegler, Türk, Wolff, Sabin, Banti and Foa. The monophyletic school, founded

* See this *Bulletin*, 1940, Vol. VIII, pp. 696-720.

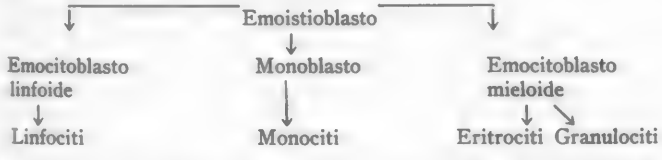
by Virchow and Wharton Jones, before the era of specific staining, was led by Pappenheim, Ferrata, Dominici, Weidenreich, Maximow, Danchakoff, and Grawitz. This school originally believed that all white blood cells were stages in a single cell type. During the evolution of their ideas, they came to regard the different types rather as parallel descendants of a totipotential, undifferentiated stem cell. This concept we owe to Pappenheim, who in 1898 described in bone marrow a markedly basophilic mononuclear stem cell from which he traced the development of the red cells and the different types of white cells. Pappenheim says that a hemoglobin-free colorless cell had been described by others as an ancestor of the red blood cells, and names Bischoff, Reichert, Remark, Kölliker, Neumann and Arnold. Pappenheim first called this primitive cell " grosser Lymphozyt " but later decided that it was a separate cell type by itself. In 1911 he stated both the usually accepted monophyletic view and his own somewhat modified stand. The standard monophyletic theory he states as follows: " dass zwar die myeloischen Gebilde nicht notwendig stets aus den lymphatischen Vorstufen hervorgegangen gedacht werden müssen, wohl aber, dass unter Umständen die lymphatischen Zelltypen in die myeloischen Lymphoidzellen und durch Vermittlung dieser in Granulozyten übergehen können." (p. 27) Pappenheim elucidates his own position: He is willing to admit that the various morphological types within the mononuclear group may be independent end-types; but he differs from the polyphyletists in that he will not commit himself to any absolute histogenetically different origin for the different types, but sees rather a common origin with different development depending partially at least upon the influences to which the individual cell is subjected as it matures. He called the common ancestor cell " Lymphoidozyt," and regarded it as the immediate ancestor of the large lymphocyte as well as of the myeloid and erythrocyte series. The monocyte he regarded as an " Altersform " of the large lymphocyte normally, and of the myeloid immature cell abnormally. In the latter case he says there are more granules in the cytoplasm of the " Altersform." These pathological forms would appear to be the abnormal myelocytes of myelogenous leukemia. Pappenheim gives a complicated scheme of his derivation of the various cell types, from his

"Lymphoidozyt" which was morphologically similar to Ehrlich's "Myelozyt." Pappenheim was a leading spirit of hematology during the first decade and most of the second of the twentieth century. He contributed the fundamental concept on which the monophyletic school still functions, contributed large amounts to the knowledge of the development of the various blood cell types, and leaves a monumental monograph on hematology which is very difficult reading and very abstruse, but in which can be found practically anything the reader may wish to know about the status of hematology in 1919, with plentiful references.

The meat of Pappenheim's views, as they have affected and influenced hematology, may be represented by the following simplified table:



The other outstanding monophyletist of this period, Ferrata, derived all of the cells of the blood from a primitive, basophilic, agranular, mononuclear cell in all respects similar to Pappenheim's "Lymphoidozyt" and Naegeli's "Myeloblast," and called by Ferrata "emocitoblasto." This "emocitoblasto" he derived from a wandering, undifferentiated "emoistioblasto," identified with primitive mesenchume, which Ferrata says is situated both in myeloid and lymphoid tissue:



Ferrata's "mieloblasto" like Pappenheim's "Leukoblast," is a definitive ancestor of the granulocyte series. In definition this is simi-

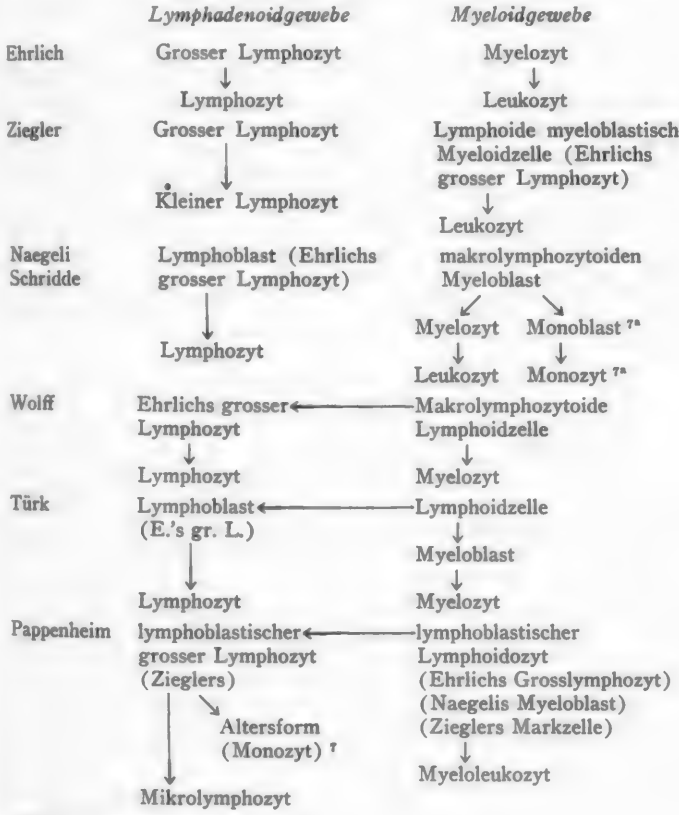
lar to Ehrlich's " Myelozyt " also, but Ehrlich believed that differentiation set in at a much earlier stage, so that morphologically his " Myelozyt " corresponds to Ferrata's " emocitoblasto " and Pappenheim's " Lymphoidozyt." It also corresponds to the lymphoblast of lymphoid parenchyma of the polyphyletists. Ferrata says that his " emocitoblasto " is an undifferentiated and agranular cell, and that the appearance of a few azurophile granules in one of these cells marks it as an early " mieloblasto." In this way Ferrata's " mieloblasto " differs from Pappenheim's " Leukoblast," which may or may not have azurophile granules. Ferrata derived the " monocito " from a " monoblasto " which comes directly from the " emoistioblasto." Ferrata has given us a monograph (1918) which is very complete, very readable, and so arranged as to be convenient for reference.

The polyphyletists lost their founder Ehrlich through his death in 1915. Leadership had been growing up in their ranks, however, and long before this time we find Naegeli already occupying a very prominent place, with Schridde, Wolff, Banti, Türk, Sabin, Ziegler and Foa. The polyphyletists postulate entirely independent origins for the myeloid and lymphoid series. For the most part they hold the monocyte to be independent of the other two types, and derive it from a variety of sources.

Naegeli believes that one must trace back all the way to primitive mesenchyme before reaching a truly indifferent cell. He introduced the concept of the " Myeloblast," an immature cell, morphologically indifferent and quite identical with the undifferentiated cells of Pappenheim and Ferrata, yet which he regards as a definitive ancestor of the granulocytes and monocytes. He believes that a few mesenchymal cells remain even in adult life for differentiation under special conditions in response to physiological demand. More will be said later of Naegeli's interpretation of the monocyte. Naegeli has given us the classic polyphyletist monograph in his *Blutkrankheiten und Blutdiagnostik*, published in at least five editions, the fifth in 1931.

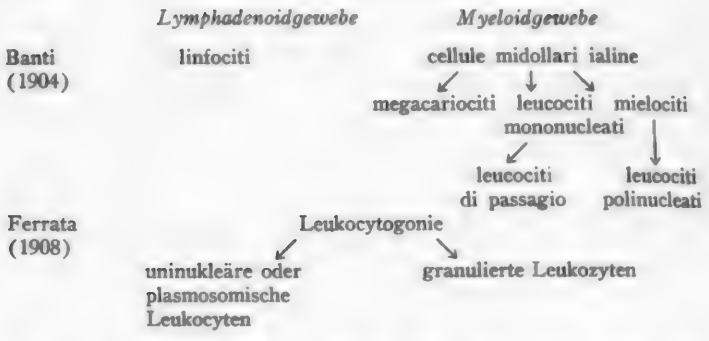
The terminology during the period we have just been discussing was extremely unstandardized. Many authors used Ehrlich's " grosser Lymphozyt " but they did not all mean the same thing by it. Such terms as " myeloiden Lymphozyten " and " lymphozytoiden

Mikromyeloblasten" make the literature a hopeless maze to the unprepared reader. Pappenheim was well aware of this, and made frequent attempts to clarify the situation. In 1908 he gave a table showing the current nomenclatures of German writers, which is reproduced here with a few modifications and the addition of the Italians Banti and Ferrata. It should be noted that Banti (1904) gives a derivation which is essentially similar to that of Naegeli. Whether this date precedes Naegeli's earliest exposition of this theory I have not been able to determine.



[7a] Incorporated from Naegeli, 1912.

[7] Incorporated from the 1911 paper; not in the 1908.



Thus we have two schools taking issue with each other chiefly over the status of the primitive cell which all have seen and described, the interpretation of which is the major point of difference. The question was, and still is, whether the so-called stem cell is totipotential and physiologically undifferentiated, retaining its embryonic character into adult life, or whether it becomes determinate and possibly morphologically differentiated, each individual stem cell being predestined to produce a certain type of mature blood cell, regardless of extraneous influences.

The Role of the Monocyte: its Morphological Differentiation

Aside from the primitive stem cell, the monocyte has been the bone of greatest contention. Various techniques have been devised for demonstrating specific properties of these cells. Michaelis and Wolff (1902) described a type of granule stainable in azure, by the use of a modified Romanowsky stain, which is present in lymphocytes, large mononuclears and the transitionals of Ehrlich. According to Ferrata there was quite a controversy over the significance of these granules, Türk believing that they were degeneration products of the cell protoplasm, Grawitz regarding them as precursors of the neutrophile and eosinophile granules, while Ferrata, Pappenheim and Weidenreich believed them to be secretion products of the cell and consequently a vital property of the cell. Pappenheim (1911) says that they are found also in myeloid cells, an argument for the monophyletists. Naegeli at first (1909) believed that the

granules of monocytes were neutrophilic, but later (1912) stated that not only are they distinct from the neutrophile granules, but also from the azurophile granules of the lymphocyte by reason of their being more numerous, finer, more constantly present, and because they give the oxidase reaction of Winkler, of which we shall speak presently. This exposition of Naegeli's in 1912 clarified the position and definition of the monocyte as well as was possible in the light of the methods and knowledge then at hand, and is to be regarded as a classic.

Schridde (1905), later confirmed by Naegeli and others, described fuchsinophile granules in fixed smears, found only in lymphocytes and arranged in perinuclear fashion. Ferrata says that Cecconi had already described these granules, but gives no specific reference. The polyphyletists regarded this granule as strong evidence in their favor, but the monophyletists immediately succeeded in demonstrating the fuchsinophile granules in the myeloblasts of bone marrow, which Schridde and Naegli themselves regarded as the precursors of the granulocytes. Ferrata ascribes this finding to Butterfield, Heineke, Maximow, Pappenheim and Weidenreich, without any specific references or dates. The fuchsinophile granules of Schridde or "Schriddischen Granula" were much discussed for awhile, but by 1920 they had practically disappeared from all but the most complete treatises.

Vital staining and phagocytosis have been the most important instrument in the study of the adult mononuclear cells. We have seen that Schultze, half a century before, had used the supra-vital method and had noted that the less granular cells phagocyted more dye particles than the more granular, also that the larger cells took up more than the smaller. Kurloff [8] and Foa, according to Ferrata, Naegeli and others, were the first to demonstrate in monocytes and transitionals granules vitally stainable in Sudan III, the so-called "Kurloff bodies," which they believed to be peculiar to these cells. Cesaris-Demel confirmed this observation in 1905. Ferrata (1906), using brilliant cresyl blue and neutral red, demonstrated large granules, surrounded by a light zone, and present only in lymphocytes. These

[8] Dates and specific references to the work of Kurloff are extremely rare; general references to him are very common. The only direct references I have found are given by the editor of Paul Ehrlich, 1914, dated 1889 and 1892 in Wratsch.

he called " corpi plasmosomi " or " plasmosomische Körper." They are interpreted by Ferrata as identical with the azurophile granules of Michaelis and Wolff. Patella (1908) believed that Ferrata's plasmosomes were droplets of degenerating protoplasm, having no relation to Kurloff bodies. He believed the mononuclears to be dead or dying endothelial cells cast off from vascular tissue. He succeeded in demonstrating Kurloff bodies and plasmosomes simultaneously by vital staining similar to that used by Ferrata. Ferrata (1908), repudiating all suggestions that his plasmosomes might be anything but vital properties of the living normal cell, proposed to call all of the uninuclears " plasmosomische Leukozyten." The Kurloff bodies and plasmosomes have remained in the active literature to quite an extent, but are not in use as standard diagnostic criteria today as are the granules stainable with neutral red and janus green. Neutral red was introduced, according to Sabin (1922), by Ehrlich for use in hematology, and its use was continued by Cesaris-Demel, Pappenheim and Ferrata, chiefly in the study of the erythrocytes. Sabin (1922, 1925) demonstrated that monocytes take up neutral red and arrange it in a rosette formation near the nucleus, so characteristically that this activity can be used as a criterion for identifying them. This is a standard method today.

Other in vivo biochemical reactions of the blood cells have contributed strong evidence in favor of the independence of the monocytes. Müller and Jochmann (1906) demonstrated in the granulocyte series a proteolytic ferment. They placed a thin layer of blood on a plate of Loeffler's serum medium and left it in the incubator for a few hours. Under each granulocyte, and under no other cells, was found a small pit. This opened up a new field. Winkler (1907) showed that both monocytes and granulocytes were able to synthesize indolphenolblue from alphanaphthol and dimethyl-paraphenylendiamine, while lymphocytes were unable to do this. This observation was confirmed by W. Schultze (1909) and others. Reference is occasionally made to a peroxidase reaction associated with the names of Bloch and Kreibach, but this seems not to have contributed anything more than to confirm the conclusions indicated by the oxidase reaction. In the later writings (Ferrata, 1918; Naegeli, 1931) these two reactions are referred to simultaneously as arguments for the same

conclusion, namely a relationship between the monocytes and the myeloid series. Bergel (1909) reported a lipolytic ferment found only in lymphocytes. This reaction is included in the arguments for the independence of the monocytes.

We have already mentioned some of the views concerning the monocyte. Ehrlich gave it an independent origin, but believed that it was transformed into the polymorph. Virchow gave it no independence whatever. Naegeli, Banti and Patella gave it a complete independence as a third type, of myeloid origin. Pappenheim, Downey, Weidenreich, Maximow, Bergel and Hirschfeld all related it closely to the lymphocyte. Ferrata is quoted as doing this, but I believe it is clear in his monograph of 1918 that he gives the monocyte an origin parallel to the lymphocytic and myeloid series from the undifferentiated " emoistioblasto." Sternberg and Kelly derived it from the adventitial cells of the lymph nodes, spleen pulp and bone marrow. Meyer and Heineke, Gruber and Türk derived it from spleen pulp and " Markstrangzellen " of lymph nodes; in fact, Türk called this cell " splenozyt."

Naegeli's important account of the monocyte in 1912 we have already commented upon. Klein (1914) studying myeloblastic leukemia, supported Naegeli's myeloid derivation of the monocyte. Evans, on the other hand (1916), found that in a case treated with salvarsan, there was a sudden increase in monocytes, without any change in the other formed elements of the blood. This he took as evidence that the monocytes arise from a source which is capable of specific and independent stimulation. Naegeli (1931) names the supporters of the myeloid origin of the monocytes as Ziegler, Jagic, Schridde, Meyer and Heineke, Crescenti, Decastello, Alder, Banti, Herz, Türk, Ferrata, and " zeitweise Pappenheim." Naegeli becomes somewhat exasperated with Pappenheim's changes of mind, saying, " Pappenheim hat im Laufe der Jahre eine Unzahl von Hypothesen über die Monoc. aufgestellt, seine Ansichten aber immer wieder verändert." (p. 149)

Embryological and Experimental Contributions to the Elucidation of the Monocyte, the Macrophage and the Primitive Blood Cell

The status of the monocyte and of the other cells as well has been further cleared up and further ramified by the work of the embryologists and experimental histologists. The pioneers of this work have been Maximow, Danchakoff and Sabin, followed in recent years by a large number of investigators, among whom Americans are for the first time preeminent. From this work has grown a new concept, foreshadowed by Mallory and Metchnikoff thirty years ago, which relates the blood cells to the various cells of connective tissue.

Mallory (1898) studied typhoid fever pathology, and described in the normal lymph node reticulum a large cell with a vesicular nucleus, possessing slight amoeboid motion and marked phagocytic properties. These he regarded as of endothelial origin, and called them " endothelial cells " or " endothelial leukocytes." In typhoid fever he found these cells to enlarge, develop an eccentric nucleus which was often indented, and his figures show many of these cells with ingested polymorphs, red cells and debris.

Ranvier (1900) studied the free cells of connective tissue. He saw them phagocyte debris and foreign matter, and believed that they provided nourishment for the tissues by breaking off bits of their protoplasm. For this reason he called them " clasmatocytes " or fragmenting cells. Marchand (1901) showed that the clasmatocytes were derived from the adventitial sheaths of blood vessels, and renamed them " adventitial cells."

Maximow (1901) placed two contiguous coverslips under the skin of a rabbit, and found that the first cells to appear between the layers of glass were white blood cells, and a little later appeared connective tissue wandering cells. Maximow called these " resting wandering cells "; others have called them " macrophages," " clasmatocytes," " histiocytes," and a variety of other names used only by a single author.

Metchnikoff (1905) made an interesting innovation in the classification of the blood cells, relating them to a generalized phagocytic system in the body. He classified the white cells under two large groups, " macrophages " and " microphages," wandering cells which

are temporarily in the blood stream, whose headquarters are elsewhere. His macrophages include fixed phagocytes of spleen, liver, lungs, etc., and free macrophages which occur in the lymphatics and are called " lymphomacrophages," and in the blood and are called " hemomacrophages." These include the larger lymphocytes and the monocytes. The " microphages " include the small lymphocytes and the granulocytes. At an earlier date (1892) Metchnikoff had given a more orthodox classification of leukocytes into four groups.

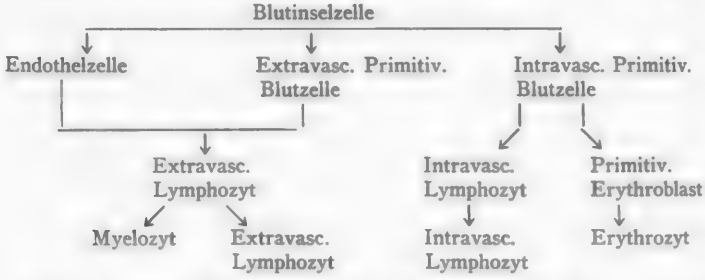
Bouffard (1906) found that when an animal was injected with dyes, certain cells stained markedly. These cells corresponded with the clasmatocytes, phagocytes, histiocytes, and endothelial cells of previous writers. Bouffard called them " cellules interstitielles," and distinguished them specifically from the cells of Kupffer. Pappenheim and Weidenreich (1908) wrote about " Speichelkörperchen " found in smears from the mouth and tonsils, which they described as " einkernige leukozytoide Gewebeswanderzellen." These they regarded as transition form between lymphocytes and neutrophiles. Downey and Weidenreich (1912) described " Solitärknötchen," cells which represent an " Übergang von Makrophagen des Reticulums zu Lymphozyten."

Aschoff and Kiyono (1913) in a classical paper, reported their results with the injection of carmine into living animals. They showed that the white cells coming from the thoracic duct did not contain any carmine, while those of the blood vessels, especially coming from the liver and spleen, showed many phagocytic cells. These cells they regarded as similar to Maximow's " resting wandering cell " and Ranvier's " clasmatocyte." They called them " Histiozyten " or " endothelien Leukozyten." They definitely included the monocytes of the blood in this group. These authors favored a triphyletic origin for the white blood cells, deriving the histiocytes from the reticulo-endothelial system. This concept of the reticulo-endothelial system was made clear in a lecture by Aschoff given in New York (1924). The subject of phagocytosis in all of its phases is reviewed by Kiyono in a monograph entitled *Die Vitale Karminspeicherung* (1914).

Schridde (1907) described in the primitive blood vessels of early human embryos a primitive cell which he called " Gefäss-Wandzelle."

He was unwilling to call it an endothelial cell, as it is less differentiated and is not a typical endothelial cell. From this cell, intravascularly, come " primäre Erythroblasten " which function as a source of blood cells for a short time only. In an embryo of 12 mm., he described extra-vascular blood forming cells, first seen in the liver, among which he could distinguish three types, " Myeloblasten," " Reisenzelle " and " sekondäre Erythroblasten," which are to be regarded as sister cells rather than daughter cells of the " primäre Erythroblasten." All these he regarded as descendants of the primitive " Gefäss-Wandzelle." Schridde is frequently quoted as believing that the blood cells are derived directly from endothelium, and the paper to which I have referred is frequently cited, but I do not agree that he claimed such a derivation.

Danchakoff (1908) described in the chick embryo an undifferentiated stem cell in the blood islands, developing extravascularly as well, and here giving rise to the granulocytes. Her paper is long, well organized and very detailed. The essentials of her scheme of hemotopoiesis in embryonic life are indicated by the following table:



Danchakoff found that blood cells or lymphocytes are produced both intravascularly and extravascularly through the fifth day of embryonic life in the chick. She found the extravascular ones giving rise to granulocytes and the intravascular to erythrocytes.

Maximow (1909, 1910) found that in mammals the same early development took place, but that the production of erythrocytes was intravascular for only a very short time. He saw endothelial cells break off and become free, and believed that these were lymphocytes, and were undifferentiated, carrying with them the potentialities of

further development. He believed that these indifferent cells were carried as such into adult life. These stem cells Maximow called "Polyblasten."

Mollier (1909) described in the embryonic liver an extravascular, mononuclear, basophilic cell derived from mesenchyme, which he called "hémogonie," and which he believed gave rise to both red and white cells extravascularly. Jordan (1917) derived a polyvalent "hemoblast" from mesenchyme directly, and also from endothelium. Ferrata (1918) believed that in early embryonic life the primitive cell gave rise to primitive erythroblasts, which at first produced only erythrocytes, but later gave rise to indifferent, totipotential "emoistioblasti," which were considered the equivalent of Pappenheim's "Lymphoidozyt" and Maximow's "Polyblast."

Simpson (1921) carried out extensive vital staining investigations on the monocytes and the clasmatocytes, and concluded that an affinity between the two types was strongly suggested.

Sabin and her associates Cunningham and Doan have contributed enormously to the elucidation of this question of the relation of the monocytes to the tissue macrophages. Sabin (1922) described the proliferation of endothelium with the elaboration of a large phagocytic cell which she had seen break off into the blood stream. These she interpreted as monocytes. She described the simultaneous production of large phagocytic cells extravascularly from the outer endothelial cells of a reduplicated endothelium. These she considered to be clasmatocytes. She says, however, that the two are interchangeable, migrating through the vessel walls quite freely. In 1925 Sabin, Cunningham and Doan add certain new observations, and modify their interpretation somewhat. They observed in the spleen the development of monocytes from the totipotential primitive cell of reticular origin. They regarded the cells arising from the endothelium as typical clasmatocytes of the blood, in accordance with their earlier observations. They also believed that the vital staining of these two types was sufficiently characteristic to make them separable morphologically. Thus they regarded the large mononuclear cells of the blood as a heterogeneous group consisting of two distinct types, clasmatocytes of endothelial origin and monocytes of reticular origin.

Bunting (1922) regarded the large mononuclear as an immature cell, found in the normal blood largely as an accident, and transforming into Ehrlich's transitional, which he regarded as a mature end-form. Normally, Bunting says, the mononuclear is a marrow cell, but under pathological conditions, such as leukemia, smallpox and measles, he believed that the mononuclears become a heterogeneous group, some of which are then derived from lymphoid origins.

Holler (1923) derived the monocyte from the reticulo-endothelial system, allying himself with Aschoff and Kiyono, and found the monocytes to act quite independently under various experimental and pathological conditions.

Ewald (1923) studied a case of very acute leukemia in which most of the white cells in the circulating blood were younger than myeloblasts. He was able to demonstrate in the marrow, spleen, liver and lymph nodes all stages of development from a primitive reticular cell to the myeloblast, all occurring in vast numbers. This type of leukemia he called " reticulo-endothelial leukemia," and he introduced a new concept of " levels of differentiation," the first being the reticulo-endothelial cell, the second the myeloblast, lymphoblast and histiocyte stage, the third the mature blood cell stage. Most leukemias he considered disorders of the second level; the reactions to infections, confined to the third level.

Lewis and Lewis (1926) with the hanging drop culture method, have found that monocytes may become identical with clasmatocytes in their vital staining and morphological properties, but they found no transformation of the lymphocytes into any other forms.

Again Clark and Clark (1930) studied the responses of blood and connective tissue cells in the web of a frog and the ear of a rabbit, and found the monocyte and the tissue macrophage to be different phases of the same cell, but saw no evidence of the transformation of lymphocytes into other forms. These conclusions were also reached by Seeman (1930) in studies on the blood of the white rat. Seeman, however, considers the monocyte and clasmatocyte to be identical.

Bloom (1928) on the other hand, cultured lymph from the thoracic duct and found that the large and small lymphocytes were transformed into large mononuclears of the inflammatory type, with fully developed segregating apparatus.

Naegeli (1931) lists seven theories as to the origin of the monocyte:

1. Lymphocytes.
2. Spleen pulp and lymph node " Markstrangzellen."
3. Endothelium.
4. Histiocytes or reticular cells.
5. Myeloblasts.
6. Adventitial cells of lymph nodes, spleen, marrow.
7. Mesenchyme directly.

The literature on this subject is endless, and I have not attempted to cover it, but only to give an idea of the present trend of hematology and the extreme activity of the field.

The Status of the Lymphocyte

Much of the work and most of the theories regarding the lymphocyte have been touched upon in the course of the discussion of the other cell types. The lymphocytes are generally considered to come from the lymphoid tissue and to enter the blood via the large lymph channels. This was the view of Hewson, and has been substantiated by many more recent investigators. The fact that the recognized primitive cells of the marrow resemble lymphocytes has caused a great deal of confusion, and the idea that lymphocytes came from marrow has been expressed quite frequently. Gulland and Goodall (1908) favored an exclusive bone marrow origin, and they are the latest to my knowledge to do this.

Bunting (1922) pointed out that there are islands of lymphoid tissue in the bone marrow, and that probably a little production of lymphocytes goes on there. Weidenreich and Downey (1912) derived the lymphocytes from the reticulum of the lymph glands, and also from the fibroblasts of the omentum and connective tissue. Danchakoff believed that in the embryo the lymphocytes were derived from a hemocytoblast, which was a primitive cell derived from mesenchyme and defined according to strictly monophyletic ideas as the precursor of all the blood cells, both red and white (1908). Downey and Thiel (1921) derived all lymphocytes directly from mesenchyme. Sabin (1922) favored a complete histogenetic sepa-

ration of the lymphocyte, on several grounds: first, that it appears much later in embryonic life than the other blood cell types, appearing first as a small lymphocyte, and definitely not elaborated in the yolk sac; second, the apparent absence of proteolytic ferments; and third, the absence of definite proof of its origin. Sabin, Cunningham and Doan (1925) feel certain that the lymphoblast can be distinguished from the primitive cell of granulocytes and from myeloblast and monoblast.

Murphy (1920) demonstrated that the lymphocytes were differentiated by a greater susceptibility to X-ray and radium radiation than any other cells. In 1919 he demonstrated a connection between resistance to tumor growth and the presence of lymphocytes, both in embryos before the lymphocytes have appeared, and in the adult in which the lymphocytes have been reduced in number by radiation. Wiseman (1931) worked out a differential age count on lymphocytes, and demonstrated a shift toward the younger forms in cases in which lymphoid hyperplasia was known to be present. He also cites McCutcheon's description of a peculiar type of motility in lymphocytes. These two phenomena he gives as evidence of the independence and maturity of the lymphocyte strain.

Doan (1932) says, "Our present information justifies both the position taken by those who have contended that 'lymphocyte-like' cells may differentiate into other specific definitive cell types, and those who have seen no evidence of transformation in a large proportion of the small 'mononuclear' round cells, which exist in the blood and tissues. Neither hypothesis may be considered as excluding the other. Those who have used the supravital and fixed techniques extensively together, each for its respective unique contribution to the problem, feel that the early precursors of the lymphocyte cycle, the lymphoblasts, may be distinguished from the 'primitive stem cell' of the white cells, and also from myeloblast and monoblast." (p. 890)

* * * *

Thus we have traced the knowledge of the blood cells from the earliest premonitions of their existence to the modern phase of the active science of hematology, confining ourselves more or less

strictly to the discoveries which have contributed to the actual classifications or to the concepts behind the classifications.

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The following bibliography contains all works which have been cited, many which were referred to in a general way, and a few which have served as background. For further bibliography on this and allied subjects, the reader is referred particularly to Naegeli (1931), Ferrata (1918), Pappenheim (1919), and the recent papers of Sabin, Cunningham and Doan; for the earlier period, Milne-Edwards (1857), and von Haller (1756).

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SOME NOTES ON THE EARLY HISTORY OF CHEMOTHERAPY

IAGO GALDSTON

Whoever undertakes to deal with the history of chemotherapy, suffers among other things the handicap of the very term chemotherapy. This term is obscure in its meaning and vague in its encompassment. According to its roots, chemotherapy should convey the meaning of the chemical treatment of disease. Such a definition, however, makes chemotherapy a synonym of pharmacotherapy. If in an effort to delimit the scope of its meaning, chemotherapy is defined as treatment by means of chemical compounds artificially produced, and not derived from plant sources, we exclude two of the earliest and most significant specifics, namely quinine and ipecac. Nor is the definition of chemotherapy offered by the man who coined the term, Paul Ehrlich, very precise. In his words, chemotherapy "treats of the action and mechanism of the effects of chemical substances upon cells and especially of drugs upon disease producing organisms."

In his *Principles and Practice of Chemotherapy*, John A. Kolmer confesses that "the term chemotherapy is difficult to define in a brief and concise manner." He then proceeds to define it several time over, without much consistency.

The historian's quest for a clear definition of chemotherapy is not dictated by the vain scruples of a punctilious grammatist. It is rather vital to his task. For as may be readily appreciated, in the light of one definition the historian will be obliged to begin his survey of chemotherapy with the dim era of primitive empiricism; while in the light of another definition he might begin with the work of Paracelsus. Again it is important to achieve a concise definition of chemotherapy in order to establish clearly the objectives of the science, this being a vital necessity to the historian who desires to determine how much of the objectives has been attained.

A definition in terms of the *objectives* of chemotherapy is offered by Dr. Claus Schillig of the Robert Koch Institute in the following terms: "The aim of chemotherapy is the destruction of the para-

sites in the body of the host, or at least to so injure them that they will prove vulnerable to the host's own defensive powers." I shall accept this definition and use it as a basis for my brief excursion into the early history of chemotherapy. Since we are here concerned with the " destruction of the parasites " it is patent that chemotherapy could not but post date the discovery of the microbic origin of disease. To begin the history of chemotherapy with Paracelsus, or with the introduction of Cinchona into European pharmacology would be, therefore, inconsistent with our premise. However, from a broader point of view, namely that of " specific treatment," chemotherapy pretending to aim at the creation of specifics, there is much of value to be gained by a critical study and comparison of the ideas and theories on specifics promulgated by Paracelsus and Sydenham with those of the pioneers in chemotherapy. In this connection I may mention Behring's " Introductory Comments on the Aetiological Therapy of Infectious Diseases " [1] as offering valuable material for such a study.

Modern chemotherapy found its pioneers among the early bacteriologists. The first recorded chemotherapeutic experiment can, I believe, be credited to Robert Koch.

In the " Mittheilungen aus dem Kaiserlichen Gesundheitsamte," Berlin, 1881 (p. 281) we find Koch's very valuable report on Disinfection. In his opening paragraph Koch observes that up to that time disinfectants had been little studied, and that equally little was known as to how, and in what different ways the disinfectants worked, *if at all*. There follows then the data of his monumental study on the variable bactericidal effects of a larger number of disinfectants employed in different concentrations and under varying circumstances. Toward the end of this report, Koch, tells of his chemotherapeutic experiment.

Koch had observed the bacteriostatic effects of bichloride of mercury in high dilution upon the spores of Anthrax cultured in vitro. " It lay near " wrote Koch " on the basis of these results to endeavor to determine whether it was thus also possible to hinder the development or to destroy Anthrax bacilli in the blood of the

[1] Gesammelte Abhandlungen von Prof. Behring. Leipzig: George Thieme, 1893 (pp. lxiv).

living animal" (p. 280). Koch was encouraged in this by a published report of von Schlesinger showing that guinea pigs and dogs, subjected to daily injections of increasing doses of bichloride of mercury, could be made to tolerate an injection of as much as 1 ccm. of a ½% solution. Koch experimented with guinea pigs. For three days he injected a guinea pig with sublimate solution. In the afternoon of the third day he inserted two silk threads carrying Anthrax spores in a skin flap behind the animal's ear. On the fourth day the guinea pig received an injection of ½ ccm. of a 1% sublimate solution. That afternoon the animal died. It was sectioned immediately, and as Koch reports "despite the sublimate injections, the animal died of anthrax." Koch repeated the experiment modifying the procedures in various ways. His results, however, forced him to the conclusion that the sublimate injections in no way affected the fatal issue of experimental anthrax infection in guinea pigs. In concluding his report Koch wrote (p. 282), "I consider this research to be far from completed, and despite the negative results, I am not inclined to abandon the belief that under certain circumstances it may be possible by means of antiseptics, to hinder the development of or to completely overcome tetanus bacilli within the body of an experimentally infected animal."

It is significant that Koch describes these experiments as being not an attempt at therapeusis—but rather as an attempt to fathom the problem of Anthrax immunity. Koch evidently hoped to attenuate the injected anthrax bacilli through the agency of the pre-injected sublimate of mercury (p. 280).

Koch's studies though failing in their immediate objectives, were fruitful in other directions. Thus his experiments prompted the inquiry as to why an antiseptic known to be so very effective in vitro, proved so very ineffective in vivo. This as is now well appreciated is a most crucial matter in chemotherapy, it having been well established that the in vitro bactericidal activity of a substance has no bearing on its function in vivo.

The early experiments in chemotherapy are intimately associated with the early studies in antisepsis, and are organically related to the science of immunology. It is not surprising, therefore, to find the names of Koch, Behring and Ehrlich closely associated. Each

was interested in sterilization. Ehrlich alone, however, persisted, being uniquely endowed as a chemist. Behring experimented with antiseptics and sterilizers for some ten years. At the end of this period he could see little promise in inner sterilization by means of artificially produced chemical compounds. He was inclined rather to rest his faith in antitoxins. Morgenroth quotes Behring as having stated that: "It can be regarded almost as a law that the tissues of man and animal are many times more susceptible to the poisonous effects of disinfectants than any bacteria known at present. Therefore, before the antiseptic has a chance either to kill or to inhibit the growth of the bacteria in the blood or in the organs of the body, the infected animal itself will be killed. The pessimism of him who declared that disinfection in the living body is for all time impossible appears to be only too justified." (Cited Walter A. Jacobs—from Morgenroth.)

This pessimistic opinion was shared by many. Inner sterilization otherwise than by means of antitoxins was regarded as chimerical. At the Congress of Internal Medicine held in Wiesbaden in 1883, it was proclaimed as the concensus of opinion that "inner-disinfection was an impossibility." (P. 3, *Zweiter Theil Gesammelte Abhandlung*, Behring.)

Despite this rather discouraging perspective, there was accumulated during this period numerous valuable data which served in later years as the very foundation of effective chemotherapy.

It is to be observed that Koch, Behring and their co-workers in their studies on the bactericidal and bacteriostatic effects of a wide variety of antiseptic substances, found that not only did the so-called antiseptics vary in their bactericidal powers, but what was rather surprising and revealing, that they also differed in their effects on different microorganisms. Thus Oscar Boer, Behring's assistant, reported that while most of the better known disinfectants such as phenol and bichloride of mercury, acted with approximately equal intensity against most bacteria, some disinfectants appeared to have a selective effect on certain microorganisms. Thus the bacilli of anthrax and of diphtheria were found to be equally susceptible to phenol and mercuric chloride, but methyl violet proved seven times more active against the Anthrax bacilli, than against those of diphtheria.

Our recitation thus far covers the decade between 1881 and 1891. This period may be considered as the tentative stage in chemotherapy. It ended in a pessimistic mood, nothing practically fruitful having issued from the studies and experiments first initiated by Koch. The following decade, that is between 1890 and 1900, witnessed but little activity in the field of chemotherapy, and yet it was during this period that the theoretical ground work was done upon which the chemotherapeutic advances of the following decade rest. To appreciate this we must take account of the dominant problems that concerned the medical research leaders during this period.

By 1890 the germ theory of the causation of disease was well established. The burning questions of the time centered around the phenomena of immunity. Pasteur had demonstrated the possibility of producing immunity by means of attenuated vaccines. Roux, Yersin, Behring and Kitassato had proved the existance of toxins and of anti-toxins. Their findings intensified the interest in the basic biological mechanisms of immunity; the problems involved in recovery from, and resistance to infectious diseases. Pasteur, it is to be recalled, advanced a rather simple theory of immunity. According to this theory, recovery in infectious disease came about when the substances upon which the bacteria fed within the host's body were exhausted. Fedor, Nuttall, Flügge and others had demonstrated that normal blood has a bactericidal power.

Metchnikoff in 1883 presented to the Naturalists Congress in Odessa, his epochal research on phagocytosis. There thus arose during the last decade of the last century two schools of thought with regard to immunity. One was the so called humoral school, the other the cellular. The humoral school envisaged immunity to be dependent upon certain properties of the blood and body fluids. These properties were believed to be innate in the blood. The cellular school in opposition contended that " the resistance of the animal body against bacterial invasion is not a fortuitous result of chemical and physical conditions encountered by the infectious agent in the blood but is rather the result of the struggle against the invasion by active forces of the body cells and fluids." (Zinsser, *Infection and Resistance*, p. 136, 2nd Edition.) " In the prolonged controversies waged with great astuteness and experimental skill, between the ad-

herents of these two schools (Zinsser pertinently observes), most of the facts which we possess regarding immunity were discovered." Within these prolonged controversies waged with great astuteness and experimental skill, there are also rooted the fundamental conceptions and the theoretical framework of modern chemotherapy.

The most active and the most eminent experimentor, if not protagonist in these controversies was Paul Ehrlich. Ehrlich was partial neither to the cellular nor to the humoral school of immunity. On the contrary he maintained that both were partially right. He "compromised" them, or better still he integrated them. In his Harben Lectures (1907), speaking of immunity effected by antibodies, Ehrlich said (p. 38), "I would here express my dissent from a prejudice which often makes itself felt, to the effect that in this matter (antibody immunity) there exists a profound contradiction between humoral and cellular immunity. As a matter of fact, to assume that the action of antibodies is merely a process of humoral pathology is to put an artificial construction on the facts observed." The Harben Lectures were delivered in 1907, and we are thus a little "ahead of our story."

Before Ehrlich could construct a theory of immunity he had need for clear and convincing explanation on the mechanisms of the morbific effects of bacteria and particularly of their toxins. To these problems, Ehrlich devoted much of his energy. His basic answers may be summed up in the words "chemical affinities." The conception of selective chemical affinities illuminates all of Ehrlich's work, including his studies in vital staining, his side chain theory of immunity, and his master work in chemotherapy. It is both profitable and interesting to trace, at this point, the development of Ehrlich's theories on selective chemical affinities.

In his short biographic study of Paul Ehrlich, Adolf Lazarus tells, that while still in the third semester of his medical studies, Ehrlich came upon a work by Emil Heubel, dealing with symptoms and disorders resulting from lead poisoning. Therein he was impressed with the preferential deposition of the metal in certain tissues of the body. The fact that the lead did not disseminate evenly throughout the victim's body, but collected in certain tissues, was to Ehrlich a provocative and fruitful realization. The realization, wrote Lazarus,

that there exists a definite affinity between body tissues and foreign substances, set the young research worker off in a direction which he never abandoned. To fathom the laws of this affinity and thereby to create new therapeutic methods was the goal of his endless labor. In the last analyses, all his work and all of his achievements are fruits of this conception.

From his uncle, Karl Weigert, he had learned to stain bacteria and tissue sections with aniline dyes. Later he employed dyes in staining living tissues. For, reasoned Ehrlich, dyes must have, even as metals do, their singular affinities for living tissues and organs. In this wise, by observing and tracing the spread, deposition and the destinies of different dyes in the living body, it may be possible to fathom the secrets of *function* in the living cells, even as by the aid of dyes, those of *structure* had been observed in dead cells. By applying his dyes (of acid and alkaline reaction) to the study of the cellular contents of blood, Ehrlich added immeasurably to this field of knowledge. He differentiated the various types of white blood cells (the phagocytes of Metchnikoff) and determined their respective sites of origin, as well as their singular predominance in varying forms of infection and inflammation. He refined current knowledge on the origin and structure of the red blood cells, and described the abnormal forms to be seen in certain types of anemia. He clearly differentiated the blood picture of pernicious anemia, from that of simple or secondary anemia. By means of dyes Ehrlich studied the oxygen requirements and oxidative functions of living cells. By injecting the dye, methylene blue, into experimental animals, Ehrlich found he could make evident the distribution of the animal's nervous system, for methylene blue has a singular affinity for the axis cylinder of the nerve cell structure. This phenomenon Ehrlich named " neurotropie." Ehrlich, together with A. Leppmann, employed methylene blue as a chemotherapeutic agent in the treatment of various forms of nerve pain (neuralgia), and against malaria.

In these early works of Ehrlich we see what the Germans call the " anlage," the foundation plans, of his later achievements, the side chain theory of immunity, and salvarsan. Here it is fitting to trace the thought behind the quest for the " therapia sterilisans magna,"

the sterilizing agent which would destroy the invading parasite but prove harmless to the host.

That certain animals are highly sensitive to, while others are entirely unaffected by, bacterial toxins, had been observed by many, including Pasteur. The explanation of this phenomenon offered by Ehrlich was rather simple. Chemical bodies, Ehrlich maintained, are inert unless they attach themselves to the body cells. " Corpora non agunt—nisi fixata." The cells of the resistant animals have no affinity for the bacterial toxins. The corpora (toxins) are not " fixata," do not become attached to the animals body cells hence " non agunt " have no affect. Proof of this hypothesis appeared to be easy. Inject the susceptible guinea pig with tetanus toxin and the toxin will promptly disappear from its blood. Why? Because the cells of the guinea pig's central nervous system have an affinity for, and hence fix (to themselves) the tetanus toxin. The animal dies. Inject the resistant pigeon with tetanus toxin, and it becomes only mildly ill. The toxin remains circulating in its blood for days. Why? Because the cells of the pigeon have little or no affinity for tetanus toxins. Toxins however are but chemical compounds complex it is true, but chemical none the less. Chemicals can be manipulated, their molecular and atomic structures can be changed. Changes in structure, spell changes in affinities. Different cells have differing affinities. Germs are cells. Germs, no doubt, have affinities for certain chemicals to which body cells have little or none. It should be possible then, to create a chemical combination for which the germ cell will have a great affinity while the body cells have little or none. Such a combination should destroy the germs and leave the body cells unharmed. The " therapeutic coefficient " of such a chemical combination would be 100 per cent. perfect. Ehrlich set out to search for such a chemical combination.

The early work of Roux and Behring gave rise to great hopes. Not a few even among the more critical workers, looked forward to the discovery of multiform antitoxins for the salvation of mankind from infectious diseases. But effective antitoxins did not issue from the busy laboratories in quite the hoped for profusion. On the contrary the yield was disappointing. The theoretical work on the mechanisms of toxin toxicity and toxin antitoxin combination, which

had been done by Bordet, Ehrlich, Wasserman and others then prompted the hope that artificial antitoxins, and more particularly chemical bacteriocides might be produced in the laboratory.

Attention was also focused on the protozoan causes of disease. Laveran had discovered the malaria parasites on November 23, 1880. Some ten days later Evans discovered the first pathogenic trypanosome. In 1901, Dutton and Ford discovered the parasites of African sleeping sickness and from this time on trypanosomes were destined to play an important role in the development of chemotherapy.

In 1902 Laveran and Mesnil, working at the Pasteur Institute, reported that they were able to temporarily clear the blood of mice infected with the trypanosome of Nagana by treating them with sodium arsenite (Fowler's Solution). This observation prompted Ehrlich to launch upon the chemotherapeutic treatment of trypanosomiasis. Having received some guinea pigs infected with trypanosomes from Nocard, Ehrlich began a systematic study of certain dye compounds. In 1904 Ehrlich and Shiga reported what must be considered to be the first modern chemotherapeutic achievement, namely the cure of an experimental trypanosome infection by means of a single dose of a synthetic chemical.

It is of little consequence from the historical point of view that this achievement was by itself of no practical value. Trypan-red, the agent employed by Ehrlich, did sterilize the blood of the experimental animals (mice) infected with trypanosoma equinum even when but a single dose was injected as late as twenty four hours before death. Unfortunately, however, as was found to be the case with other chemical compounds in other infections, trypan-red failed to exert similar therapeutic effects on other animals or with other types of trypanosomes. What is, however, historically significant in this work of Ehrlich and Shiga is the fact that it represents the first attempt *to create* compounds with definite parasitocidal powers. In this work, Ehrlich followed his guiding idea, that of selective affinities. Laveran, in his experimental treatment of trypanosomiasis, had employed Fowler's Solution, a well known arsenic compound. Ehrlich in contrast began his experimental studies by employing a series of commercial dyes. He found one dye showing

some activity against the trypanosomes. Trypan-red was then synthesized as an analogue of this dye and upon trial it was found to possess greatly enhanced trypanocidal properties. Trypan-red in the words of C. H. Browning thus became " the first effective synthetic substance discovered as the result of purposive investigation."

This experience served as an intense and enduring stimulus to the quest for chemotherapeutic specifics. Ehrlich and his co-workers developed other dye compounds which proved even more effective than trypan-red. Many workers were drawn into the field and publications soon appeared " thick and fast." Important observations were reported. Significant among them were the following two. Trypan-red had little or no effect on trypanosomes outside the animal body. Parasites it was found could become resistant that is drug-fast to chemotherapeutic agents.

In 1905, Schaudin discovered the spirochete cause of syphilis. Ehrlich then turned his attention to this infection, and as is so well known achieved there his greatest triumph. It will be recalled that Laveran first showed that Fowler's Solution had an effect upon trypanosomal infections. Thomas, working in the Liverpool School of Tropical Medicine employed in 1905, an organic compound of arsenic and found it to be even more effective against trypanosomes than Fowler's Solution. The arsenic preparation used by Thomas was known as atoxyl. It had been prepared in 1863 by Bechamp by the action of arsenic acid on aniline. In 1902 Blumental employed the sodium salt of this preparation in animal experiments and, finding it to be less toxic than the inorganic forms of arsenic he named it atoxyl.

Ehrlich became interested in atoxyl because of its effectiveness in trypanosome infections. He analyzed the compound and determined its true composition. He then set about manipulating its structure and testing the resultant compounds therapeutically. In this work Ehrlich found a link between trypanosomiasis and syphilis in the spirochaete-like organism of rat-bite fever. The latter infection being extremely refractory was utilized by Ehrlich as a sieve, a " cribrum therapeuticum." The compounds found to be most effective against the spirochaete of rats were tried out in rabbits with spirochaete pallidum lesions. It was in this way that arsphenamine

was discovered in 1909. Ehrlich believed that in arsphenamine he achieved a " therapia sterilizans magna." He saw in arsphenamine the salvation of mankind—from one of its fierce plagues, hence in his laboratory arsphenamine was named " Salvarsan."

During the years in which Ehrlich accomplished his vast research work he managed, also, to formulate his theoretical conceptions of the principle and mechanisms of chemotherapy. He was guided in his labors by clearly conceived theories and plans. The core of both was selective chemical affinities. As late as 1911 Ehrlich defined the objectives and mechanisms of chemotherapy in the following words: " wir die parasiten chemisch abzutoten (versuchen) " and " nur solche substanzen, die von den parasiten aufgenommen werden konnen, konnen auf die selben abtotend wirken." (" We aim to destroy the parasites by means of chemicals " and " only such substances as are taken up by the parasites can act upon them lethally.") The latter is a paraphrase of Ehrlich's dictum " corpora non agunt nisi fixata."

As was to be expected Ehrlich's theories strongly dominated the field of chemotherapy. His work and his achievements inspired hundreds to labor in the field of chemotherapy, but the yield of their labors was meager. Fifteen years after the discovery of arsphenamine one encounters in the literature a distinct note of frustration. Ehrlich's basic theories are now being questioned. The outlook especially with regard to the chemotherapy of the bacterial infections, is in 1923 and even in 1935 rather " gloomy."

In his address before the Harvey Society in 1923, Walter A. Jacobs said: " In his theoretical considerations to explain the action of chemotherapeutic agents, Ehrlich assumed a direct action of the substance, of its alteration product, on the parasite. He conceived of this action as being brought about by the avidity of certain groups or chemoceptors in the cell of the parasite for certain groups contained in the chemical. By assuming these discrete affinities within the cell the attempt was made to give more visible expression to certain phenomena which were observed in the reaction of microorganisms to chemicals containing certain groups in the molecule." *But on the whole workers no longer agree that such precise definition can be given to the relationship between chemical constitution and*

therapeutic action. . . . " In regard to the general outlook for the chemotherapy of bacterial infections it may be said that at the present date available seem quite barren of suggestions. . . . " " The real difficulty lies in the necessarily opportunistic experimental method and the lack of a rational scientific means of approach. The problem is essentially a search for a substance of unknown nature but which must yet perform a service by a mechanism of which we are equally uncertain. It may be possible to inquire successfully into what biological properties such a substance must possess, or under what biological conditions it will have to operate; but such information will not point to the substance itself. In the case of bacterial infections, experience has presented us with too few points of contact between our knowledge of chemical structure and whatever biological properties may be required in the exhibition of a therapeutic effect to present a rational basis for the search for curative substances. Perhaps the real solution of the problem may be ultimately found by gaining an insight into the chemical nature and mode of operation of the substances which are normally elaborated by the organism in its fight against infection."

In 1935, Prof. C. H. Browning, in his Presidential address to the Royal Medico-Chirurgical Society of Glasgow summed up the yield of thirty years of world wide research in chemotherapy as amounting to " four distinct antimalarials—six groups of trypanocidal compounds—many new antiseptics and an almost miraculous spirochaeticide."

Associated with the early history of chemotherapy are the names of many men, not mentioned in this paper. I have said nothing of Guttmann who with Ehrlich first employed methylene-blue in the treatment of malaria; nothing of C. H. Browning who studied the drug fastness developed by parasites; and nothing of Morgenroth who with Levy developed in 1911, the compound Optochin a derivative of quinine which for a time looked like a specific against pneumococcal infections. I have thought it best and more profitable to devote the time available to tracing the development of the guiding ideas of chemotherapy rather than to a recitation of the numerous fruitless and of the few fruitful labors of a very larger number of men. The latter would be an enormous task. The literature of

chemotherapy is unbelievably large. Beside it is my conviction that the medical historian should concern himself primarily with ideas, and with works only insofar as they are the vehicles and tests of ideas. In that perspective Ehrlich is seen to be the colossus of chemotherapy. He it was who formulated the theories upon which research in chemotherapy was conducted for almost forty years. To my knowledge though there have been dissenters, none has come forth with a substitute theory for Ehrlich's "selective Affinities." That Ehrlich's theories are faulty, that his dicta are defective is now, I believe, quite evident. Perhaps the new triumphs of chemotherapy will serve as a basis for better theories on its mechanisms.

THE DECLINE OF TUBERCULOSIS, WITH SPECIAL REFERENCE TO ITS GENERALIZED FORM *

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The waning of an endemic disease is an impressive event in medical history, although one only dimly appreciated by the professional historians. The giant decline of tuberculosis is unlike anything else in the story of disease. From a time when a quarter of all deaths were due to tuberculosis the most progressive states of the world have come to a period when the toll is less than a twentieth of the total mortality. The disappearance of leprosy in many parts of the world is perhaps the closest approach. The leprologist Ernest Muir[1] has called leprosy characteristic of one stage of civilization and tuberculosis of another. The disappearance of leprosy from Europe still mystifies. It has been attributed to the quarantine principle, itself an outgrowth of the translation of the Bible (Muir), the enormous destruction of lepers by bubonic plague (Sigerist[2]), and to many other factors. Plague itself, like typhus, cholera and the other great epidemic diseases, has struck quickly and almost as quickly gone. Small-pox tumbled from its high place with the rapid adoption of vaccination, and typhoid fever dropped sharply with an engineering achievement, proper sewage disposal. Tuberculosis has declined slowly but steadily.

Its origins are obscure, but of the seriousness of the disease from the dawn of human history there is no doubt. Its presence in the early centuries is attested by records in Egypt, China, India and elsewhere, and even proved by direct observation of the residues of tuberculosis in ancient Egyptian mummies, and, while its share in the total morbidity cannot be figured for each age of the past, an

* The William Snow Miller Lecture delivered at the University of Wisconsin under the auspices of the Alpha Pi chapter of Phi Beta Pi on March 25, 1940.

[1] Muir, Ernest, The Control of Leprosy, Amer. Jour. Trop. Med., Vol. 17, 1937, 51-58; International Journal of Leprosy, Vol. 6, 1938, 233-239.

[2] Sigerist, Henry E., Der Aussatz auf den Hawaiischen Inseln, Verhandlungen der Schweizer. Naturforschenden Gesellschaft, 1932, pp. 452-453.

extensive occurrence may be deduced from the description of cases by the early medical writers. The accounts in ancient Greece and Rome are of typical chronic pulmonary tuberculosis, in clinical course altogether like that of today, with wasting, cough, expectoration, blood spitting and fever, with periods of improvement, often long course and final sinking. Under the hygienic and housing conditions of the times such a disease, being infectious, would be wide spread.

One of the best attempted reconstructions of the course of tuberculosis in history is that by Allen Krause [8] in the Herman Biggs Memorial lecture of 1927. In broad outline Krause indicated the probable history as follows. The disease was widely prevalent in the cities of the Greek and Roman civilizations. With the disruption of the Western Empire in the fifth and sixth centuries decentralization of population took place in Western Europe, with migration from the cities and the development of separate and widely dispersed agricultural economies. Communities were small and transportation poor. The conditions for rapid transfer of infection were lacking, and probably the total incidence of tuberculosis decreased greatly. In the craftsman industrialization of the Middle Ages centralization of population recurred, with the building of many small walled towns, intensely crowded. Presumably under such conditions tuberculosis increased rapidly. From then until the present century it must have been endemic in all civilized countries, with high mortality.

The maximum morbidity from tuberculosis in England apparently occurred about 1780, when the recorded mortality rate for "consumption" was 1120 per 100,000 population. The peak was coincident with the early development of what in later years was designated the "industrial revolution," and it appears that the history of tuberculosis has repeated itself with respect to the industrial revolution in all other countries. The first effect has always been a rise, soon followed by a fall in the tuberculosis rate. In London the figure dropped to 716 in the decade 1801-10 and to an average of 567 for the years 1831-35. The improvement is credited to amelioration of the bad working conditions which were brought about by the early

[8] Krause, A. K., Tuberculosis and Public Health, Amer. Rev. Tuberc., Vol. 18, 1928, 271-322.

rapid industrialization, and to other development of social measures for the relief of poverty and distress. In America the industrial revolution came later than in England and the peak in incidence of tuberculosis and its subsequent decline were correspondingly delayed. In colonial times tuberculosis was apparently only an urban disease. The mild industrialization of the 1830's caused an influx in the towns, but without significant rise in the tuberculosis rate. The heavy immigration of the middle years of the century diluted the population with fresh stock of rural home origin. The tuberculosis rate apparently dropped correspondingly, only a rise in grim fashion with the great intensification of industry and flocking to the cities of the East that occurred in the 1880's. After that, as in England, hygienic conditions were improved and conscious effort was made to relieve the distressing conditions created by the first rapid expansion of factory production, and since then the tuberculosis rate has dropped.

No serious objection has ever been made to the following statement by Robert Koch [4] in the article announcing the discovery of the tubercle bacillus. "If the number of victims that a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infectious diseases, such as bubonic plague, Asiatic cholera, etc., must rank far behind tuberculosis. Statistics teach that one-seventh of all human beings die of tuberculosis, and that if one considers only the productive middle age group, tuberculosis carries away one-third, and often more, of these."

Indeed fairly reliable statistics indicate that in large centers of population in past years tuberculosis often accounted for a fifth or even a quarter of the total deaths. A century ago in America the well known Philadelphia physician Samuel George Morton,[5] in the first American text on pulmonary tuberculosis, quoted the following rates for large American cities as the proportion of tuberculosis deaths to total mortality in the decade 1820-1830: 1:5.2 in New York, 1:5.5 in Boston, 1:6.4 in Philadelphia and 1:6.2 in Baltimore. Allowing for the inaccuracy of the records, we must still admit an enormous extent of tuberculosis at the time.

[4] Koch, R., The Aetiology of Tuberculosis. Translation by Berna Pinner and Max Pinner, Amer. Rev. Tuberc., Vol. 25, 1932, 285-323.

[5] Morton, S. G., Illustrations of Pulmonary Tuberculosis, Key and Biddle, Philadelphia, 1834.

Tuberculosis has long since ceased to be the first cause of death in this country, and its decline has become a subject of the greatest interest not only as an index of the progress of mankind, but as a basis for prediction of the future. Within the last few years eminent statisticians, long restrained by caution, have at last freely predicted a virtual disappearance of the disease in this country.

The story of the decline of tuberculosis could be told from many points of view, most directly perhaps by statistics. But it may be of more interest to trace the history, even sketchily, in its other aspects, including the changing views on its cause, the long road to its understanding, its variable character and the final shift in emphasis from an individual to a public health problem.

The waning of tuberculosis, apparent in all countries with advanced civilization, has been less spectacular than the conquest of other diseases, but has meant a greater change in the well being of the population, and a greater rise in its average longevity, than the eradication of any other. Under way at least a century ago, it has continued with only occasional interruption to the present. The factors responsible have been lengthily debated, and the influence of specific antituberculosis measures seriously questioned. In more recent years, however, there has been little argument against the claim that organized antituberculosis campaigns have at least definitely accentuated an already favorable process. It is probably a fair statement that, if the antituberculosis campaign is not yet responsible for the decline of tuberculosis, its organization is so powerful, and its principles so sound, that it must inevitably become so.

The present directive effort is based upon a hard won understanding of the principles of spread of the disease. In 2300 years of medical writing on tuberculosis only fifty have been seriously concerned with its spread as an infectious disease, and for little more than a decade has the conception been held that it is possible to live in a civilized community and escape infection altogether.

Dim perceptions of the contagious nature of tuberculosis were not rare in the early history of tuberculosis study. Just as today it is good pedogogic practice to include in an etiological list all the causes that might conceivably later prove to be the correct one, so most of the early writers from Aristotle to Richard Morton somewhere made

reference to contagion as a possible element in the acquisition of phthisis, although few seem really to have believed in it.

For some reason the Italians and Spaniards took the view most seriously. Laennec,[6] a non-believer himself, wrote " Phthisis is contagious in the opinion of a few laymen and a few physicians of the South." But the Republic of Lucca at the opening of the eighteenth century, and other Italian cities and Spanish cities shortly afterward, passed stringent laws making consumption a reportable disease and requiring the destruction of clothing and articles once used by a consumptive. The great Italian pathologists Valsalva and Morgagni followed the local view and avoided post-mortem examination of tuberculous bodies as dangerous. This view was not generally shared, however, and the English particularly scouted it. With the latter it was more than a matter of academic difference of opinion. A hundred years ago, as today, the Englishman with chronic lung disease sought the more sunny climate of the Italian peninsula for winter comfort, and it was a serious inconvenience to be harassed by legislative interference. John Keats, who died of consumption in Rome in 1821, was forced to have all his supplies pulled up through a window. The penalty for dying of consumption in Italy was almost prohibitive. The London Lancet in an editorial[7] in 1867 frankly accused the Italians of more cupidity than science: " It seems that the Italians have conveniently imbibed the notion that consumption is contagious, and should unhappily a phthisical patient die in an hotel, the bill but too often contains the singular item, *Indemnite pour réfaction des meubles et de la chambre occupe par la defunt, £100 sterling.*"

In most of the world for more than twenty centuries tuberculosis was considered the result of an inherent constitutional trait. The advance of modern understanding of tuberculosis is often dated from Sylvius de la Boë,[8] who doubtless expressed the current best medical view of the seventeenth century, and one handed down from the early Greek philosophers, when he wrote about 1670, " Since experience shows that while families are so disposed to consumption that

[6] Laennec, R. T. H., Cited by Gerald B. Webb, Tuberculosis, Paul B. Hoeber, Inc., New York, 1936.

[7] Editorial, The Lancet, Death Fees in Foreign Hotels, Vol. 1, Mar. 9, 1867.

[8] Sylvius de la Boe, Franciscus, De Phthisi, Amsterdam, 1674.

few of their numbers escape, it may well be asked in what does this phthisical constitution consist? It is notorious that the complaint is hereditary, and passages from parents to children, but the nature of the disposition is not well understood." He himself, impressed by the age incidence of phthisis, attributed the disease to change in the body fluids with increasing age. Into the various ramifications of his views we need not go. Fundamentally, erroneous or not, they had much in common with modern theories of internal secretion. It is worth while to note that in spite of his humoral theories he made substantial advance in solidist pathology. He was an experienced morbid anatomist and to him we owe the first clear correlation of caseation in lungs and lymph glands, or, in brief, phthisis and scrofula, and recognition of the sequence of caseation, liquefaction and cavity formation in the lungs. How anatomical understanding grew with Morton, Stark, Baillie, Bayle, Laennec and Louis is too familiar a story to merit repetition.

With Laennec begins the modern period. His contribution was the unification of all tuberculosis. It was a great achievement to put in a single compartment pathological processes so diverse as nodular tuberculosis, caseo-pneumonic consolidation and massive excavation of the lungs. It was not to go unchallenged, and the controversy between Virchow and the followers of Laennec on the unity of the events leading to phthisis was one of the great medical debates of the nineteenth century. Virchow [9] regarded the tubercle as a lymphoid neoplasm, the evolution of which might end in caseation, calcification or resorption. But in his view caseous pneumonia had nothing in common with the genuine tubercle. Like the latter it might indeed end in pulmonary excavation and phthisis, but in origin caseous pneumonia was, in his opinion, the result of a non-tuberculous acute inflammation.

The rush to Virchow's support by lesser compatriots at the very time when Villemin [10] was proving the correctness of Laennec's views seems now almost ludicrous. Virchow's conception was put forth in mature form in 1865. Villemin made his famous pronouncement

[9] Virchow, Rudolf, Die krankhaften Geschwülste, August Hirschwald, Berlin, 1863.

[10] Villemin, J.-A., Etudes sur la tuberculose, Paris, 1868.

before the French Academy of Medicine in the same year, but delayed publication *in extenso* until 1868. Felix von Niemeyer [11] in 1866 thought all was settled when he followed Virchow in writing: "The dangerous tenets of Laennec's doctrine that pulmonary tuberculosis . . . can never develop out of the acute or chronic pneumonia, or arise from a bronchial hemorrhage, or from a neglected or protracted cold . . . have in practice a most pernicious effect on the prevention and treatment of phthisis. Laennec's dogma that every form of phthisis is caused by a new growth, and that the cavities in the lung originate alone in the softening and evacuation of this growth was simply a pathological hypothesis which more recent research in pathological anatomy has entirely refuted." In the succeeding fifteen years the Virchow-Niemeyer view was itself entirely refuted, and much of the fatal opposition came from Germany itself.

The early opposition to Villemin was at first almost as great, and none was more violent than that of his compatriots. The hysterical outburst of Pidoux [12] expressed the general first reaction. "Experiments on animals," cried out Pidoux, "give such and such results and you, instead of controlling them by clinical experiments and by all the accepted facts of human physiology, construct upon them a general theory of human tuberculosis and all diseases! For it you upset all the ideas already acquired. We must accept over night that phthisis falls from the clouds and that in its pathogenesis, the subject himself, habitus, hygienic surroundings, heredity and diatheses are of no account; that all depends upon an impossible tuberculous virus originating without doubt in a tuberculous individual who had it from some other individual and so on to the first man, who, however, had it from nobody at all and must have created it himself out of nothing."

After Villemin the best known name in the field of inoculation experiment is that of Cohnheim. Others anticipated his work, just as Villemin's own experiments were anticipated, but we must admit

[11] Niemeyer, Felix von, Clinical Lectures on Tuberculosis. Translation by C. Baeumler. Publications of the New Sydenham Society, London, 1870.

[12] Pidoux. From Calmette, L'infection bacillaire de la tuberculose chez l'homme et chez les animaux, translation by W. B. Soper and G. H. Smith, Williams and Wilkins Co., Baltimore, 1923.

that history does a sorry job in the recognition of priority, and shall not pause to discuss the element of fortune in scientific discovery. In 1882 the tubercle bacillus was discovered and one phase in the understanding of tuberculosis was concluded.

One might have expected a prompt capitalization of the new knowledge of infectiousness in the control of phthisis. Actually this was long delayed. To be sure, the discovery was followed by a flood of literature on the manner of contagion. Sputum was easily seen as the carrier of the disease. Cornet calculated that a patient with advanced pulmonary tuberculosis might expectorate seven billion bacilli a day. A heated controversy arose between Cornet and Flügge on the respective dangers of sputum in the form of droplets and dried dust. At the same time the distinguished von Behring,[18] of antitoxin fame, announced the competing view that pulmonary tuberculosis is alimentary in origin and " the milk fed to infants is the chief cause of consumption " in later life. The rôle of bovine tuberculosis in the disease of man was later clarified, and advantage taken of the acquired knowledge, as we shall note in this paper, in the virtual extinction of bovine tuberculosis, and its concomitant infection of man, in the United States.

But progress in the control of infection in man was held up by the discovery that most adults had been infected with tuberculosis. Anatomical proof for this fact was presented in abundance in the opening years of the present century, and was soon supported by the specific diagnostic tuberculin skin test. The view developed that infection was inevitable. What mattered was resistance.

Throughout most of this period a decline in prevalence of tuberculosis was taking place without any specific efforts to foster it. Indeed the decline was probably unrealized, because reliable mortality statistical analyses, so common today, were not yet in vogue.

However, a conscious antituberculosis campaign of a sort came with the great improvement in diagnosis at the opening of the century. The percussion method of Auenbrugger, eighteenth century discovery, left for exploitation by the nineteenth, and Laennec's method of mediate auscultation, provided physicians with weapons

[18] Behring, E. von, The Suppression of Tuberculosis. Cassel Lecture. Translation by Charles Bolduan, John Wiley and Sons, New York, 1904.

in which great confidence was placed. Refinements in physical diagnosis of chest disease accumulated throughout the century, and clinicians became extraordinarily skilful in the recognition and delimitation of pulmonary tuberculosis. With the advent of X-ray chest photography in the opening years of the present century, a method of immense importance came in, about which the antituberculosis movement of the future seems to center. With it the lesions so skilfully delineated by physical diagnosis became visually perceptible, and the tendency to rely upon X-ray diagnosis, with or without physical diagnosis, has grown. The older physicians lament physical diagnosis as a lost art, and shake their heads at the decay in medical standards, just as the skilled craftsman deplores the advance of the machine age. To this the roentgenologist retorts by an impressive assemblage of minimal tuberculosis that escapes recognition by the keen touch of physical diagnosis, but is caught by the X-ray.

In all probability the bulk of tuberculosis diagnosed in the past on the basis of physical examination was moderately or far advanced. This was not through any fault of the physicians concerned, although it may be assumed that only the masters could detect the earliest changes due to the disease, but chiefly because the disease is insidious in onset, or its onset, if acute, is more plausibly interpreted in some quite different way. In any event the bulk of tuberculosis recognized as such in the first three quarters of the nineteenth century was of such nature as to give only the most unfavorable prognosis. Abundant records could be cited indicating the belief, held by the medical profession and lay public alike, that tuberculosis was a fatal disease.

All physicians, of course, recommended a long list of drugs, which were generally applied and from which the poor patient had no recourse. It was a time when a drug was seldom dropped, although it was a routine procedure to add one. Of the lengthy list perhaps only cod liver oil has survived.

Sanatorium treatment, which started in the second half of the nineteenth century, is now based on the principle of fresh air and rest. At its outset it was indeed an expression of faith in fresh air, but it was in part an extension of the principle of exercise. The first notable sanatorium, established by Hermann Brehmer in 1859, was set in Goerbersdorf not only for the clean mountain air, but also

for the convenience of exercise. Gradually in the development of the sanatorium fresh air was more, and exercise was less stressed. A period was reached, described by Alfred Henry as one of " fresh air at any cost." This period coincided in part with one of unbelievably heavy feeding of patients.

All the time the value of rest became more apparent, and has finally become the cardinal principle in the treatment of tuberculosis, whether it be the general treatment of the patient, or the local treatment of his lungs by the current semi-surgical procedures.

The development of sanatoria has been the most notable feature in the directed control of tuberculosis up to the present time. In America alone in 50 years from the establishment of Trudeau's sanatorium in the Adirondacks in 1884, sanatoria have increased from one to 600 with a bed capacity of approximately 95,000. Yet only 32 years ago William Osler [14] wrote " At present we are in the sanatorium phase of treatment . . . and have learned very important lessons in the management of cases. But the disease is so widely prevalent that we can never hope to place sanatorium treatment at the disposal of more than a very small percentage of the patients. The brunt of the battle must be borne by the practitioners at large."

A few years later the Framingham experiment, a project for the demonstration of tuberculosis control, set up in Framingham, Massachusetts, financed by the Metropolitan Life Insurance Company, and administered by the National Tuberculosis Association, established principles for determining the magnitude of the tuberculosis problem. An outgrowth of the Framingham demonstration and similar projects, was the standard of one bed for the treatment of tuberculosis for each annual death in any given community. This was soon recognized by public health agencies as inadequate for the desired rapid subjugation of the disease, and many communities have long since surpassed this standard. States with the most active programs are now trying to achieve a ratio of 2 beds per annual death from tuberculosis. In New York State in 1939 there were 6447 deaths from tuberculosis, according to provisional figures, and 15,416 beds,

[14] Osler, William, Historical Sketch in Tuberculosis, Arnold C. Klebs. D. Appleton and Company, New York, 1909.

or more, are available for tuberculous patients. Thus the ratio of beds to annual deaths is 2.4 in this state.

The decrease in community infection effected by the utilization of 95,000 beds by tuberculosis patients is incalculable. The sanatorium has been primarily an institution for restoration of tuberculous patients to health, but from the public health point of view the sanatorium and tuberculosis hospitals have functioned, in effect, as voluntary quarantine stations for the isolation of patients with infective sputum. Sanatorium construction is continuing in the United States, but no faster than its apparent need. It has become an established public health practice to seek out unrecognized cases of tuberculosis, and provide facilities for recovery, and the practice is doubly valuable, for it reduces the unrecognized spread of infection at the same time. In a few more years the result should be knowledge of the location of almost all of our tuberculous sick, with residence of most of them in specially provided hospital or sanatorium facilities. Under such conditions tuberculosis will be detected in its early stages, and will relatively rarely be of fulminant character. However, we cannot yet anticipate the early eradication of tuberculosis. Even if an adequate case finding program covered the country, and proper provision of beds were made for patients with open disease, and all patients who should do so availed themselves of the opportunity, tuberculosis would still last years as a community problem because of the length of life of survivors with the disease. This may be looked upon as the modern phase of tuberculosis, a chronic disease, under organized control.

In this very sketchy picture of the decline in tuberculosis no attention has been paid to its different clinical forms, and no prediction of the future is justified unless such consideration is given. Success is largely predicated on decreasing severity of tuberculosis, and the fact remains that acute tuberculosis is still a problem. Rapid forms are seen in the Negro to a much greater extent than in the white race, and are still relatively common. However, all over the world there is evidence of increasing chronicity in Negro tuberculosis. Apparently all peoples when subjected to tuberculosis pass from a period of acute disease when the disease is new to one in which the lesions are chronic, and to those criteria of the progress of civilization in a

community, based on the nature of disease in its midst (see Muir in the first paragraph of this paper) we may add the character of its tuberculosis. Indeed very roughly the advance of civilization in a people may be traced as follows in the pathological succession in the character of its endemic tuberculosis:

1. Acute generalized tuberculosis.
2. Chronic generalized tuberculosis.
3. Chronic pulmonary tuberculosis.

The history of the first two periods is instructive for our understanding of the third. The second and third are comparable. In broad aspect, the white race has emerged from the second period and entered the third. The colored races are in the process of emerging from the second at present. Their transition is more rapid than has been that of the white race. They have the advantage of all the recent knowledge, denied the white race, in affecting the change. In the following pages a sketch will be given of the decline of generalized tuberculosis. It may be prophetic for the decline of the localized pulmonary form.

The Decline of Scrofula

In popular conception tuberculosis is pulmonary tuberculosis, but every medical student learns in his second year, if not before, that most organs of the body are susceptible to the development of tubercles. As the disease exists in the United States, at least 90 per cent of fatal tuberculosis is restricted to the lungs and their contiguous anatomical structures. This view omits, of course, the tiny tubercles detectable by minute search in the other large organs in any case of advanced pulmonary tuberculosis. Approximately ten per cent of our fatal tuberculosis is listed on the death records as non-pulmonary. In more than half of this, however, viz., in cases listed as intestinal tuberculosis, miliary tuberculosis and tuberculous meningitis, the disease is primarily pulmonary. Accordingly, something less than one-twentieth of our mortality from tuberculosis is the result of the diseases outside of the lungs. The chief seats of this sort of disease are the bones, lymph nodes, kidneys and genital apparatus, the serous membranes and the skin.

It is probably fair to assume that the same rough parallel exists be-

tween morbidity and mortality from these forms of tuberculosis as in the case of pulmonary tuberculosis. We may, therefore, conclude that a twentieth or less of the tuberculosis of the living also is essentially non-pulmonary.

In past history, however, the figure was vastly different. In times and places tuberculosis in its chronic generalized form, including the lungs, or restricted to organs outside the lungs, has been exceedingly common. These forms of tuberculosis in the past have been comprehended under the broad term " scrofula."

Why tuberculosis should at times be restricted to the lungs and at other times be widespread throughout the body, has been the subject of intense and continued technical research. In general it may be said that wide prevalence of scrofula has corresponded directly with four factors, which overlap, viz.:

1. A stage of hygiene in the population favoring massive infection.
2. Recent introduction of tuberculosis.
3. Prevalence of bovine tuberculosis and the drinking of infected milk.
4. A high rate of pulmonary tuberculosis.

Scrofula and Current Hygienic Practice

We may begin with the first of these. A thousand years ago in a period when, all are agreed, hygienic consciousness was slight, probably no disease was more common. There is abundance of reference to scrofula in medical and non-medical literature. There are even illustrations to help us evaluate the records. Our knowledge comes from the fascinating history of the King's Evil and the royal touch for this condition. The origins of the ancient custom need not be here recalled. Before Christ the royal touch was believed to cure disease, and after Christianity was established, especially among the Frankish kings, the custom was clothed in a supposed divine authority. A time came when the king's touch became considered specific for scrofula and supposed related conditions. The old records state that Robert the Pious of France (996-1031) cured external sores by laying his hands upon them, but the sores are not identified.

Some years later, however, Philip I (1061-1108) and Louis VI (1108-1137), as recorded by the Abbe de Nogent, touched patients "afflicted with scrofulous swellings about the throat or in other parts of the body (Scrophas circa jugulum aut uspiam in corpore)," to relieve them of their affliction.

In England Edward the Confessor (1002-1066) carried the practice on, and soon bitter and extended controversy arose as to whose was the divine right, the kings' of England or the kings' of France. In any event the monarchs of each continued the custom, with occasional intermissions, to the reigns of Queen Anne in England and Louis XIV in France. And even if the Republican investigators in Paris in the Age of Reason found only five cures among the 2400 patients touched by the unfortunate Louis XVI, enough faith remained to induce Charles X of the succeeding short-lived empire to revive the custom at his coronation in 1824, and it may be added that the patients for this occasion were presented by no less distinguished surgeons than Alibert and Dupuytren. The details of this extraordinary history may be read in the scholarly monograph of Raymond Crawfurd.[15]

Into the success of this method of treatment we need not go. It is enough to note that when the choice lay, as Crawfurd points out, between purging with strong cathartics, application of "externals to discuss, suppurate or extirpate the glands . . . extirpation by manual operation, escarotick or caustical medication" and the painless laying on of the king's hands, most patients preferred the royal touch. We may add that many physicians of note gave personal and statistical support to the efficacy of the treatment, and leave the responsibility with them.

For our purposes it is necessary to satisfy two queries: were the ailments for which the kings touched really scrofula, i. e., tuberculosis in its superficial or generalized form, and, secondly, was the volume of these royal clinics a reliable index of the prevalence of the disease?

On both of these questions there is considerable light. The touching was originally for two types of illness, swollen glands and inflamed eyes. These two lesions soon became synonymous with

[15] Crawfurd, Raymond, The King's Evil, Clarendon Press, Oxford, 1911.

scrofula, and there is no question that a huge amount of non-tuberculous ophthalmia was included. It is probable that to this day, because of this ancient tradition, tuberculosis of the eye is over-diagnosed. But of the generally tuberculous nature of the swollen glands there can be little doubt. At a time when plague was rife a few mild cases of that disease were counted scrofulous; so likewise with the adenitis of syphilis, and presumably also the other lymphoid hyperplasias that are familiar today. But the discharging character, the long course, the association with caries of the bones and the location, all lead us inevitably to the conclusion that the affliction was in large part truly tuberculous adenitis. A manuscript picture of Edward the Confessor touching the neck of a young woman, and the clear pictorial delineation in Queen Mary's Manual of the Queen, with her index fingers on the upper posterior cervical nodes of a kneeling boy, could hardly represent anything but the treatment of scrofula.

On the number of patients touched there is also much information. It was not a rare thing for a king to treat a thousand patients at a single healing. Doubtless many of these were " repeats," although fully half of those touched in these ceremonies would attest healing within a short time and should therefore not have returned. Beyond question the piece of gold that went with the touch led many unafflicted to enter the lines for monetary profit. However, guard was set against imposture, as Andre Laurent, physician of Henri IV (1609) recorded, by the passage of the royal physicians between the rows, for examination of each applicant and assurance of his actual illness. Altogether, thousands upon thousands of patients with unmistakable scrofula must have been touched by the many kings addicted to the procedure. It is stated that Charles II touched 92,000 persons in the two decades 1662-82. In 1682 alone he is said to have touched 8577 persons for the King's Evil, and this was a time when assemblage was difficult because of poor transportation, and the population was far below what it is today.

With the seventeenth century began the accumulation of pathological records about which there can be no question, and with this period came the first recognition of the underlying similarity of scrofula and phthisis. Prior to this time medical observation was largely restricted to the surface of the body. Even then the associa-

tion of scrofulous lymph glands with the coughing and blood spitting of consumption was too frequent to escape note. But with Franciscus de la Boë Sylvius [8] (1614-72), a German-born Frenchman who became a doctor in Switzerland and practiced medicine in Holland, and the Englishman Richard Morton (*c.* 1635-98), to mention but two of the better known investigators of the time, the essential identity of the cheesy degeneration of the lymph glands of patients with scrofula, and the cheesy nodules in the lungs of consumptives, that were prone to soften and form cavities, was discovered. Richard Wiseman [16] in 1676 left one of the most widely cited descriptions of the clinical characteristics of scrofula, noting its relation to phthisis. The final proof of the relation of the two came with the inoculation experiments of the French army surgeon Villemin in 1865, which answered the question of the infectious nature of tuberculosis, and actual isolation of the germ itself in 1882 by the German bacteriologist Robert Koch.

The records of this long period are of much interest for the curious views once held on the etiology of this affliction, and it will not be out of place to record a few. In each successive medical age etiology was interpreted, naturally, in the light of the current medical vogue. When the vaguer humoral pathology gave way to the more sharply specified principles of the iatro-chemical school, the explanations of scrofula followed the current medical trend. When diseases were explained in terms of Rokitansky's dyscrasias, scrofula shared in this type of explanation. Through it all an attempt was made to link scrofula with other ailments. During the dominance of the medical opinion of the Old Vienna School the dictum of de Haen that scrofula arose from an alteration of the body fluids resulting from small-pox, was widely accepted on the Continent and in England. With the progress of inoculation for small-pox and advent of vaccination some writers predicted a rise, others a fall, in scrofula. Elaborate statistical correlations were drawn on the coincidence of scrofula and the acute contagious diseases of childhood, which seemed only to prove that almost everybody had both types of disease. A continued effort was made to establish a correlation with syphilis. The distinguished

[16] Wiseman, Richard, Chirurgical Treatises, London, 1676.

French clinician Lugol, now chiefly remembered for his iodine solution, drew a connection between the two, and in a philosophical mood credited the decline of Spain as a world power, variously attributed by others to abstraction of colonists, expulsion of the Moors and Jews, the Inquisition, the imbecility of the court, and even the publication of Don Quixote, to wide prevalence of scrofula consequent on the introduction of syphilis. A less dramatic writer in another country attributed scrofula to the introduction of the Irish potato. The most constant association to which attention was drawn was, as indicated, with phthisis.

In the meantime, in spite of gathering knowledge, scrofula remained one of the most prevalent of diseases. It was all of infectious origin, as we now know, but how much could be attributed to the predisposing influence of low hygienic standards, and how much to recency of introduction and to bovine tuberculosis remains to be answered. We may dismiss recency of introduction at once in a disease endemic for a thousand years. In the time of Edward the Confessor, and, presumably, long before that, scrofula continued in a dreary succession of generations. The principle of natural selection had had time in abundance to eliminate any especially susceptible stock. The question of milk infection is less easily dismissed, although it is unlikely that the hordes of downtrodden poor of the Middle Ages and subsequent centuries ever had much milk, least of all that the slum children of the great cities like London and Paris where scrofula was endemic, were as universally favored with milk as they were afflicted with scrofula. However, bovine tuberculosis is old—there are references to it in the Talmud, and what may be so interpreted even in the early Mosaic law—and milk in some form, boiled, fermented or fresh, has always been a staple article of diet with rural peoples. From earliest times it was recommended for invalids, even for scrofula itself. Its virtue in consumption was extolled in the famous "Regimen" of Salerno. Altogether it is probable that for centuries a significant proportion of scrofula has been the result of drinking cow's milk infected with tubercle bacilli. The actual proportion must have varied greatly in different societies.

But that the vast amount of medieval scrofula was not all of milk origin can be deduced from the following facts. In countries like

England and Scotland, where both scrofula and bovine tuberculosis are still all too prevalent, the proportion of all cases of scrofula that can be attributed to the bovine type of tubercle bacillus is much less than 50 per cent, according to the well known figures of Griffith, Blacklock and others, although it may average higher in children. This leaves a significant proportion due to the human type bacillus.

Moreover, in certain countries where tuberculosis has existed for centuries and relatively little milk is drunk by the masses, and that commonly boiled, scrofula is widespread. China is such a country. A recent writer, Korn,[17] has reported a study of 1200 cases of tuberculosis in Chinese, of which approximately half were of the scrofulous type. In hygienic standards China today must have much in common with Europe of the Middle Ages. Chinese clinicians tell us that tuberculous adenitis is far from rare in the upper classes where the hygienic level is highest. But in certain customs like the use of a common eating bowl, unhygienic practices are involved which may place the more favored classes on a par with the lowest as respects the transmission of infection. The common eating bowl is believed largely responsible for the tremendous explosion of tuberculosis, much of it scrofulous that occurred with the advent of the white man in the South Seas. Chiefs and their lowliest followers, visiting sailors and beach combers, democratically gathered at the various feasts, dipped their fingers in sticky poi, sucked them off with relish, and returned them, saliva-coated, to the common bowl. Here infected milk could not have been a factor, because little milk was consumed. But one man's sputum could infect many people, and the actual result was a tremendous amount of tuberculosis of the acute scrofulous type.

Not to labor the point too long, a correlation is evident between low hygienic level or bad hygenic practice, leading to massive alimentary tuberculous infection, and the prevalence of scrofula. There is every reason to believe that the scrofula in Europe in the middle ages was to a considerable extent the result of continual massive infection dependent upon the unhygienic practices of the time. The decline in scrofula that has occurred must be correspondingly dependent on

[17] Korns, J. H., Tuberculosis in China, Amer. Rev. Tuberc., Vol. 18, 1928, 323-335.

the improvement that has followed in the manner of living and the removal of the opportunities for massive infection.

Scrofula and Recent Introduction of Tuberculosis

When tuberculosis is newly introduced in a people, several of the factors listed as predisposing to the generalized form of tuberculosis are in operation to favor its spread. In the first place such people are generally primitive people living at a low hygienic level. In addition, since the principle of natural selection has not yet operated, the genetic stocks present presumably include some of low resistance to the generalization of tuberculosis. When tuberculosis first strikes the population, the more susceptible members are carried off most promptly. The massive generalized type of tuberculosis, scrofula in its acute form, is common. After a time the principle of survival of the most fit comes into play, and in the residuum the disease is more chronic.

Many illustrations of widespread scrofula, following shortly after the first planting of tubercle bacilli in a people could be cited. Brief reference has been made to the introduction in Polynesia. Cummins [18] has written at length of the arrival of tuberculosis in African tribes. He speaks of a typical tribe as in " a geographical state of isolation which remains unbroken from generation to generation until, one day, the tribe is found out by some traveller or missionary and is gradually absorbed into an increasing civilization. In such a tribe " he writes, " there must exist, previous to the coming of the Europeans, a state of unrestricted multiplication of persons without the power to defend themselves against tuberculosis. . . . In these circumstances the strains of people unable to resist are likely to reach as high a level or higher than those born with an adequate power of protecting themselves against the germ." The result of introduction in such a group is generally considered to be a high initial mortality with rapid annihilation of the more susceptible stocks, followed by a period of tuberculization of the remainder, and a high incidence of tuberculosis of more chronic character.

An experience closer at hand, in America, well illustrates the usual

[18] Cummins, Lyle, Primitive Tuberculosis, John Bale Medical Publications, Ltd., London, 1939.

train of events. It concerns the Indians of the great plains of Canada and has been put on record with unusual clarity by Ferguson,[19] who wrote " no natural experiment among civilized people has approximated the intensity of these Indian epidemics." In 1880, following the extinction of the buffalo, the plains Indians were crowded into newly created, restricted reservations. Contact was close, hygiene was bad, and tuberculosis, a new disease to the great majority of these nomads, had been introduced. Under the conditions exposure must have been frequent and intense. A veritable epidemic of tuberculosis occurred, with mortality reaching a peak of 9000 per 100,000 in 1882.

Very significant was the speed with which certain families were wiped out by the disease. Within three generations half of the family trees died out. Tuberculosis was a very important, although not the sole factor in the family extinction that occurred. Ferguson attributed the variation in family survival to inherent difference in resistance to tuberculosis rather than such environmental factors as food, housing and sanitation, which were uniformly bad. In the succeeding half century a great drop in tuberculosis mortality followed (from 9000 per 100,000 in 1882 to 270 per 100,000 in 1932). This certainly was not all the result of elimination of highly susceptible stock. Living conditions improved much in the meantime. But in light of the appalling initial mortality, with a high percentage of the deaths from 1882 to 1902 due to tuberculosis, as Ferguson relates, it is hard to believe that natural selection was not an important factor. Many similar natural experiments are reported in the literature.[20]

The character of the disease was as interesting as its severity. All types of tuberculosis were seen. The scrofulous type was exceedingly common. During the first two decades of the epidemic a third of the school children had swollen caseous and discharging glands. In some schools it was recorded that almost every child had discharging glands. Soon, however, the prevalence of the disease regressed. In

[19] Ferguson, R. G., The Indian Tuberculosis Problem and Some Preventive Measures. Transactions of the 29th Annual Meeting of the National Tuberculosis Assn., 1933, p. 93. See also Cummins, Lyle, *loc. cit.*

[20] Hall, G. A. M. and C. P. Chang, Latent Pulmonary Tuberculosis in Chinese Adults of the Professional Classes, Amer. Rev. Tuberc., Vol. 30, 1934, 193-208.

1932 the rate of scrofulous infection in school children had dropped to one per cent.

The mode of transmission of the scrofulous type of tuberculosis merits comment. Under the conditions of modern hygiene, which have largely eliminated contact infection, but still freely permit airborne infection, the transmission of disease from a patient with nonpulmonary tuberculosis has become rare. But under primitive conditions, with a minimum of sanitation, apposition of healthy tissue with the discharges of suppurating glands and feces and urine of patients with generalized tuberculosis is frequent and makes direct contact infection common. As a matter of fact Simes and Paynter [21] found the excretion of tubercle bacilli frequent in the very Indian boarding school children of Ferguson's report.

Scrofula and Bovine Tuberculosis

In a population long subject to tuberculosis in spite of a high level of hygiene, the continued presence of scrofula calls for special comment, and the question of alimentary infection through milk must be given careful consideration. In the British Isles tuberculous lymphadenitis of more or less generalized character has been common for centuries. The vast amount of writing on the subject from the earliest manuscripts to modern times can be explained only on the basis of a widely prevalent disease.

Its frequency in England in the middle of last century may be seen from figures like those given by Glover [22] in the Fothergillian prize essay of 1846. In a workhouse in Kent were 78 boys, of whom all had scrofula, and 94 girls, of whom 91 were scrofulous. An investigation was made. Some relation was noted with goiter, but more stress was laid on the fact that in this and other workhouses the more confined workers seemed the most susceptible. The diet was subjected to some scrutiny, but a weekly ration of sixty ounces of bread, twenty-three of flour, fourteen of oatmeal, six of meat, half

[21] Simes, A. B. and L. E. Paynter. A Study of the Occurrence of Virulent Tubercle Bacilli in the Excreta of Tuberculous Indian Children, Tubercle, Vol. 15, 1934, 498-503.

[22] Glover, R. M., On the Pathology and Treatment of Scrofula, Fothergillian Prize Essay for 1846, John Churchill, 1846.

a pound of potatoes and seven and a half pints of milk, seemed to the investigators adequate provision for any child of nine. It would seem to us a little short in both protein and fat, and perhaps unappealing in other ways, but without going into the hardships of the English orphan of a century ago, we may pause at the item milk. Can we attribute some of the scrofula of the time and place to two glasses of milk a day?

How widespread bovine infection was a century ago is difficult to determine, but there is every reason to believe it was as common then as now. It is still widely prevalent in the British Isles, and in spite of control efforts of some intensity, a large amount of infected milk still finds its way to market. In 1921 McFadyean calculated that 40 per cent of the principle milking breeds were tuberculous. In a report of the Ministry of Health in 1931 this figure was considered too low to represent the facts. Obviously all infected cows do not yield infective milk. The Ministry of Agriculture concluded that from 1.0 to 1.5 per cent of cows in herds in which the disease was discovered gave milk containing tubercle bacilli. The process of pooling or "bulking," however, multiplies the danger. In Manchester in 1929 9.8 per cent of 1133 samples of milk were reported to contain tubercle bacilli; in London 7.5 per cent of infected samples were found.

As late as 1936 there were communities in Scotland in which from 40 to 90 per cent of herds were infected. In one area in Banffshire 15 out of 53 milk cows had tuberculosis of the udder. Griffith [23] who was a member of the Royal Commision, appointed in 1911 to study bovine tuberculosis, in commenting on the situation wrote, "Twenty-six years have passed and the country still has a milk supply infected with tubercle bacilli to such an extent that from 5 to 12 per cent and more of samples of ordinary churn milk contain tubercle bacilli, and more than a third of the milking cows of the country are tuberculous."

In such a situation protection can be afforded only by efficient pasteurization before use, and pasteurization is a recent procedure. Even today much infective milk is consumed, and British figures continue to indicate a high incidence of bovine type infection in

[23] Griffith, A. S., Bovine Tuberculosis in Man, Tubercle, Vol. 18, 1937, 529-543.

lymph node, skin, bone and joint, and genito-urinary tuberculosis. The prevalence of bovine infection in the past was presumably at least as great.

No account of the decline of tuberculosis can omit mention of the remarkable achievement of the United States in wiping out bovine tuberculosis. In the face of strong initial opposition, but later with general approval, the United States Department of Agriculture has fostered a steady campaign of tuberculin testing of cattle and slaughter of those found infected. From figures varying from 3-5 per cent in all cattle and 5-50 per cent in dairy cows, in different parts of the country in the early years of the present century, the proportion of infected cattle has dropped to less than half of one per cent. Since the bulk of milk sold has the added safeguard of pasteurization, the opportunity for bovine type infection of man is now exceedingly restricted. The most recent results (Van Es) [24] show that bovine type tuberculosis in children has fallen far below the figures recorded by Park and Williams in 1910, which have been widely quoted in text books. In 1930 it seemed that not more than 3 per cent of the non-pulmonary tuberculous lesions of childhood were of bovine origin. The percentage presumably has continued to drop since that time. In the United States tuberculosis in man, due to the bovine type of tubercle bacillus, is indeed fast becoming a vanishing disease.

It is thus probably true that some of the drop that has occurred in the incidence of clinical lymph node tuberculosis can be attributed to the disappearance of bovine tuberculosis. However, a still more important factor remains to be considered.

Scrofula and Pulmonary Tuberculosis

In countries with a very high incidence of pulmonary tuberculosis scrofula also is common. Such was Europe until a century ago. Such is China today. As we have seen, in such countries more than one factor of the several listed as correlated with scrofula, may apply, and the separate roles can but with difficulty be unravelled.

[24] Van Es, L. and Martin, H. M., The Incidence of Avian Tuberculosis in Mammals other than Swine, Research Bulletin 49, University of Nebraska, College of Agriculture, Agricultural Experiment Station, 1930, p. 1.

However, in America in our own time we have seen a great drop in the incidence of scrofula that can be attributed largely to a single and simple factor. That is the decline in pulmonary tuberculosis. Although the two may be dissociated, tuberculosis of the lungs and generalized tuberculosis of lymph nodes are often concomitant, and in such cases the latter is often the sequel of the former. A drop in the incidence of pulmonary tuberculosis, therefore, will be accompanied by a fall in the number of cases of tuberculosis of the lymph nodes.

The spectacular decrease in scrofula in the United States in the last 30 years is apparently on this basis. It is part of the general decline of tuberculosis. An interesting study by Thompson [25] was suggestive in this respect. It is well known that hospital admissions for scrofula are far fewer than was formerly the case. The disease also appears to be less conspicuous in special tuberculosis clinics. Thompson made a direct test by comparing the incidence of cervical lymph node tuberculosis in 5000 consecutive admissions in a large tuberculosis clinic in 1935 with that in 1000 admissions in the same clinic in 1905, making the comparison especially in cases of pulmonary tuberculosis. He found that the majority of cases of cervical lymphadenitis were in patients with pulmonary tuberculosis, and that in patients with pulmonary tuberculosis the per cent with cervical lymphadenitis was the same in 1935 as in 1905. Allowance was made for the proportion of white and Negro patients.

However, it must be recalled that the total mortality from tuberculosis, and in a general way the morbidity, are only a quarter of what they were in 1905. A decline of three-quarters in the incidence of pulmonary tuberculosis has had a profound effect on the incidence of scrofula. Add to this the virtual abolition of bovine type infection in the United States, and the explanation of the " disappearance of scrofula " [26] seems at hand. Admittedly, other factors enter into the explanation, including that of nutrition, which on the average has improved greatly in the same length of time.

Today we appear to be observing a last stand of scrofula in the Negro race. Again we are confronted with an overlapping of causes

[25] Thompson, B. C., Tuberculosis of Cervical Lymph Nodes, Amer. Rev. Tuberc., Vol. 37, 1938, 410-419.

[26] Landis, H. R. M., The Disappearance of Scrofula, Amer. Rev. Tuberc., Vol. 21, 1930, 195-201.

in the relatively high incidence of the scrofulous type of tuberculosis in this race. In the first place the Negro is far closer than the white man to the period of first introduction of tuberculosis. The factor of natural selection toward the more chronic localized type has not operated over as long a period as in the white. Equally or more significant, however, is the fact that pulmonary tuberculosis is far more common in Negroes than in whites. If scrofula is four times as common in Negroes, it must not be forgotten that pulmonary tuberculosis, which may lead to generalized tuberculosis of lymph nodes, is three or four times as common also. When the rate for pulmonary tuberculosis in the Negro reaches the relatively low rate of the white population today, it will be surprising if there is not a corresponding decrease in the scrofulous form of the disease.

In conclusion we may return to the disappearance of scrofula as an index of the progress of civilization. It has been said in the foregoing pages that endemic chronic generalized tuberculosis may be related to the opportunities for massive alimentary infection in the current state of hygiene, the recency of introduction of tuberculosis in the population and the incidence of pulmonary tuberculosis. Taking them up in order, we may note that those conditions favoring massive alimentary infection, whether with bovine or human type bacilli, are disappearing everywhere and have almost vanished in our own country. As respects the second factor, the races of the world vary. They are in different stages of a process loosely called racial immunization, which is in large measure really natural selection toward chronic localized rather than generalized tuberculosis. Most of the white race has long been exposed to tuberculosis and probably already derived what benefit it may expect on this score. Finally the decline in scrofula is closely related to the great decline in phthisis. Although they are often pathologically independent, chronic generalized tuberculosis is frequently but a continuation of pulmonary tuberculosis, and as the latter declines scrofula tends to disappear with it. The summation of the several factors in preceding generations has made scrofula almost a disease of the past. Comparable progress in future generations may be anticipated, leading to the virtual eradication of pulmonary tuberculosis, an endemic disease characteristic of our recent hygenic level, just as scrofula was of the hygenic level of the past.

THE FRIENDSHIP OF WILLIAM WITHERING AND ERASMUS DARWIN *

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George II sat on the throne of England and in France the poignant pen of Voltaire was portending a new era when a son was born to Edmond and Sarah Withering in Wellington. The year was 1741 and the boy was named William. The child was of good lineage; Edmond, his father, was a successful physician and his mother was the daughter of Dr. George Hector who delivered Samuel Johnson. William Withering received an adequate education from his early youth, first from his erudite father and at twenty-one he entered Edinburgh University. There Withering sat at the feet of some of the most distinguished scholars of the day. John Hoke unfolded to him the wonders of the vegetable kingdom and created in him his insatiable fondness for botany. On one of Withering's annual returns to Edinburgh during his student days, history records that on going through York he became acquainted with the distinguished apothecary, Thomas Fowler, after whom Fowler's Solution was named.

Young Withering was the proud recipient of the degree of doctor of medicine in 1766. His inaugural dissertation was entitled "Malignant Putrid Sore Throat." Opportunity was not slow in rapping on the door of the embryonic physician. At Stafford he accepted a post as physician in charge of an infirmary built for the indigent.

In addition to the numerous duties incumbent upon his new post at Stafford, Withering continued his interest in botany. This love of flowers started with the instruction young Withering had received under Hoke at Edinburgh and was intensified by his friendship with Richard Pulleney, historian of British botany and first English

* Third in a series of Medical Friendships.

biographer of Linnaeus. Singularly enough one of Withering's first patients, Helena Cook, was interested in flower painting. During her entire convalescence Dr. Withering collected wayside flowers to satisfy the artistic propensities of his patient. Not only did this give Withering extensive experience among the wild flowers of England but also secured for him a wife, for later he married Helena Cook.

Withering's activities were variegated, he was extraordinarily versatile and quite gregarious. His interests were not confined to the field of botany, he made studies in the fields of geology and mineralogy. The mineral, barium carbonate, bears its name, Witherite, owing to the ubiquitous curiosity of this physician. He was known to his close associates as a collector of antiques and he established quite a reputation as an antiquarian. Withering was a member of an amateur dramatic club interested in Shakespearian productions. His proclivities extended to music for he took part in musical gatherings and performed well on the flute and bagpipe. Besides, he had an insatiable love for poetry.

These early years in medicine replete with achievement at Stafford were interrupted by a letter from a doctor, an Edinburgh graduate ten years his senior. Erasmus Darwin, distinguished medical practitioner, informed Withering of an opening with greater opportunities in the industrial center, Birmingham. In 1775, nine years after his graduation, Withering moved to Birmingham. Here the two physicians met in intimate association. Withering was admitted to the Lunar Society founded by Erasmus Darwin. This remarkable organization of erudite scholars met monthly in the homes of its members in the town of Birmingham. Here Withering was associated with the elite scholars of his day. Outstanding among the members of the society were James Watt, the inventor of the steam engine, Joseph Priestley, the discoverer of oxygen and nitrous oxide and the famous maker of pottery, Josiah Wedgewood. Many distinguished visitors attended the meetings of the Lunar Society including Herschel, the astronomer, and Benjamin Franklin.

The friendship of Doctors Darwin and Withering continued for many years. As practitioners each enjoyed a wide reputation and extensive practice. Years after his coming to Birmingham it is said

that Withering's practice was the largest in the community and some observers are of the opinion that a jealousy developed between the two physicians. Rather it is to be interpreted as a wholesome quest on the part of each to carry the art of healing to as many of the sick as possible. In the Lunar Society the duress of busy practice was dismissed. The pursuit of knowledge, the eagerness of intensive research and wholesome fellowship united these indefatigable savants in a tie that was inseparable.

In 1776, Withering was treating two to three thousand indigent cases a year. He was sought widely as a consultant. Benjamin Franklin wrote him from Paris requesting his advice on the formation of urinary calculi. He traveled over muddy country roads in his light carriage, constantly making botanical and mineralogical notes, to visit his widely distributed patients. During the severe epidemic of scarlet fever which occurred in 1778, Withering had a wide and exhausting experience in the treatment of the disease. He published an account of his observations entitled, "An Account of Scarlet Fever and Sore Throat or Scarlatina Anginosa."

Despite the prolific and varied character of Withering's activities, undoubtedly the greatest contribution that he made to posterity was his use of the purple foxglove in the treatment of dropsy. How he gained knowledge of the secret formula of Mrs. Hutton who had employed an herb concoction containing digitalis successfully in the treatment of the edema of the Principal of Brazen Nose College at Oxford has been reiterated many times in the literature and depicted in art in the charcoal pencil drawing by E. L. Chase entitled, "Golden Sovereigns for the Secret of the Wayside Flower." Withering's investigations were thorough, his clinical observations were substantiated by animal experiments on turkeys. These studies led to the publication of that medical classic in 1785, "The Foxglove and an Account of Its Medical Properties."

The life of Dr. Darwin moved rapidly along paralleling the life of Withering and vies with it for fullness and versatility. Despite Darwin's corpulence which he developed in early life, his small-pox marked face and careless attire, he was possessed with a winsome nature which attracted to him many friends. While Withering was concerned with botany, mineralogy and the therapeutics of digitalis,

Darwin spread his fertile mind over much of the scope of human knowledge of his day. He was undoubtedly an inventive genius. He invented a speaking machine, an artesian well, a horizonal wind mill and a surveying machine. While these practical turns of his mind gave fruition Dr. Darwin speculated in luminous music, electricity, the phonograph and methods of improving the climate and for the last named his home gave him ample opportunity for betterment. Pearson in his biography of Erasmus Darwin suggests that there is scarcely an invention in the world today that the fertile mind of this English savant did not foresee.

And thus with indefatigable energy these two intellectual dynamos sped on. The younger Withering found his health slipping in 1783 in his 43rd year. Pulmonary tuberculosis made it necessary for Withering to abandon work and go to the country estate of Matthew Boulton for recuperation. Withering's strength failed—a lingering illness at Fairhill and a rapidly diminishing strength prompted someone to comment "The Flower of English Physicians is Withering." He died in 1799. And today the purple foxglove which proliferates over his grave at Edgbaston makes immortal the Flower of English Physicians.

Darwin lived to see his seventy-first birthday in 1802, indefatigable to the end. Out of his marriage with Mary Howard was born Robert Darwin, who married a daughter of Josiah Wedgewood. On February 12, 1809, the same day and year on which Abraham Lincoln was born, a son, Charles, was born to Robert Darwin, destined by fate to inaugurate a new order in biology. And so as one pushes back the curtains of the past the Origin of the Species and the treatment of auricular fibrillation have a common bond in the friendship of Erasmus Darwin and William Withering.

MEDICO-HISTORICAL NEWS AND ACTIVITIES

American Association of the History of Medicine

Dr. George Sarton has just accepted an invitation to deliver the *Fielding H. Garrison Lecture* at the Seventeenth Annual Meeting of the Association which will be held in Atlantic City, N. J., on May 4-6, 1941.

The Association will hold a fall meeting on October 7, 1940, in Cleveland, Ohio, under the auspices of its constituent society, the Ohio Committee on Medical History and Archives with Dr. Howard Dittrick as local chairman. The morning session will be devoted to the presentation of papers. In the afternoon members of the Association will have an opportunity to visit the various collections of the city and to see demonstrations. A dinner session with several papers will close the meeting.

The Association regrets to announce that it lost a Past President and one of its most active members, Dr. David Riesman, who died on June 3 at the age of 73. An obituary and a bibliography of Dr. Riesman's historical writings will be published in a later issue of the *Bulletin*.

National News

New York, N. Y.

The exhibition of the works of Leonardo da Vinci, held for over a year in the Palace of Arts in Milan, Italy, is being brought to the United States. Eighteen large roomfuls of material pertaining to his life and work, including working models of his inventions and his works of art, were shipped on April 30 on the *Barberigo* from Genoa. The exhibition will first be shown to the American public at New York's Museum of Science and Industry in Radio City and will be opened to the public in the early part of June.

Three years were spent by the Italian Government in assembling the exhibition, many items of which, such as the fourteen volumes of Leonardo's original autograph writings and his studies for works of art lost or unfinished, have for centuries remained in private collections. Models of one hundred and seventy of Leonardo's

scientific inventions, which range from an apparatus for measuring the earth to a heat-operated roasting oven, have been constructed. All these inventions, including his plans for flying machines, his submarine, his differential gear for vehicles and other features of modern life, conceived 400 years ago, will be represented by full-size or scale models made from his own drawings and specifications, which will be exhibited together with the models themselves.

One of the features of the New York exhibition, according to Robert P. Shaw, director of the museum, will be the actual operation of the Leonardo models. His printing press will be operated as in his own day, and his mint, made at the behest of the Medici, will turn out such coins as were minted for the Florentine Republic 400 years ago.

San Francisco, Calif.

The Osler Club of the University of California Medical School.

Drawn together by a common interest in medical history and the men who contributed to it twelve members of the sophomore class of the University of California Medical School met on April 19th to form an Osler Society. From each succeeding sophomore class will be selected new members until a limit of forty has been reached. The society will meet four times a year, when papers will be read by members on topics pertaining to the life of the late Sir William Osler as well as to subjects relating to medical history. Some time during the year there will be a banquet at which the principal address will be given by an authority on either Osler or on a subject in medical history.

The plan of the organization is to follow along the tradition of the Osler Society at McGill Medical School; this has served as a model for the many similar societies already in existence both in this country and in England.

It is hoped eventually that all Class A Medical Schools will make the history of medicine of sufficient interest to the students that an Osler Society will be a very essential asset to the medical curriculum.

It is not for the facts of medical history alone that one encourages this study among medical students but that the life of Sir Wil-

liam Osler may be an inspiration to every medical student that he may live up to the highest in the code of the ancient and honorable guild of physicians.

E. ROSENCRANTZ.

Toronto, Ontario.

The Canadian Medical Association meeting in Toronto the week of June 17th has arranged for two meetings of the Section of Historical Medicine, one session to be held at the convention hotel where all sections are meeting, the other at the Academy of Medicine where there will be exhibits of interest.

The program includes:

Section of Historical Medicine

Chairman, Dr. Jabez H. Elliott
Secretary, Dr. John Ross

Wednesday, June 19th

(Osler Hall, Academy of Medicine, 13 Queen's Park, Toronto)

2.15 p. m.

Postage stamps of medical and paediatric interest—Dr. T. G. H. Drake, Toronto.

The Klotz library—Dr. W. L. Holman, Toronto.

Bucke and Osler; a personality study—Dr. Geo. Stevenson, London.

Indian medicine in western Ontario (illustrated by medicine songs)—Dr. Edwin Seaborn, London.

Shakespeare's son-in-law, Dr. John Hall—Dr. E. P. Scarlett, Calgary.

Exhibits

(a) To illustrate papers read:
   1. Postage stamps of medical and paediatric interest.
   2. The Klotz library.

(b) Academy exhibits of interest to visiting physicians:
   1. The Osler collection of prints and engravings.
   2. The Academy's Osleriana.

3. The "Johnston Cabinets" with microscopes and slides used by Johnston, Bovell and Osler.
4. The collection of lecture cards, medals, diplomas, instruments, etc., of early Ontario doctors.
5. The collection of medical book plates.

Thursday, June 20th

2.15 p. m.

The iconography of Theodore Turquet de Mayerne—engravings and portraits (lantern slides)—Dr. Thomas Gibson, Kingston.

Military medicine, long ago, yester-year and tomorrow—Dr. Léo Pariseau, Montreal.

A doctour of phisik—Dr. Heber Jamieson, Edmonton.

Natural philosophy during the reign of King Charles II—Dr. A. G. Nicholls, Montreal.

The history of fractures in Canada (lantern slides)—Dr. J. H. Couch, Toronto.